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CONTENTS AND SUBJECT INDEX

Carcinoma in the First Three Decades of Life. Norman Hall, M.D., and James W. Bagby, M.D., St. Louis....703

The Treatment of Schizophrenia with Metrazol by the Production of Convulsions. Isidore Finkelman, M.D., Chicago; D. Louis Steinberg, M.D., and Erich Liebert, M.D., Elgin, Ill....706

Inflammatory Strictures of the Rectum Associated with Venereal Lymphogranuloma. Carleton Mathewson Jr., M.D., San Francisco....709

Mental Symptoms Associated with Brain Tumor. Moses Keschner, M.D.; Morris B. Bender, M.D., and Israel Strauss, M.D., New York....714

The Testing of Activity of Childhood Tuberculosis. W. Ambrose McGee, M.D., Richmond, Va...718
Discussed by Drs. Stafford, Linde and McGee.

Audiometers and Hearing Aids. A. A. Hayden, M.D., Chicago..723

CLINICAL NOTES

Thrombocytopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid). Arthur M. Hoffman, M.D.; Julius Kahn, M.D., and J. P. Fitzgibbon, M.D., Los Angeles....725

Thrombocytopenic Purpura Following Use of Allyl-Isopropyl-Acetyl-Carbamide (Sedormid). A. M. Moody, M.D., San Francisco..726

SPECIAL ARTICLE

The Chemistry of Thiamin (Vitamin B_1). Robert R. Williams, D.Sc., New York....727

THERAPEUTICS

The Therapy of the Cook County Hospital: Icterus (Jaundice). Edited by Bernard Fantus, M.D., Chicago, in collaboration with Dr. Frederick Steigmann....732

COUNCIL ON PHYSICAL THERAPY 740

COUNCIL ON PHARMACY AND CHEMISTRY 740

COUNCIL ON FOODS 741

EDITORIALS

Virus Infections....742
Proteins of First Importance....743
Epilepsy....744

CURRENT COMMENT

Cancer in Early Life....744
Physical and Emotional Periodicity in Women....744
Dermatophilic Poliomyelitis....745

BUREAU OF LEGAL MEDICINE AND LEGISLATION 765

(Subject Index on next page)

ORGANIZATION SECTION
Facing page 774

Suggestions on the Conduct of a Study of Medical Care....127B
Developments in Workmen's Compensation Since 1930....131B
Graduate Medical Education: V. Minnesota....136B
Medical Legislation....137B
Woman's Auxiliary....140B
Medical Economic Abstracts...140B

A.M.A. SESSION—San Francisco—JUNE 13-17, 1938

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SUBJECT INDEX TO THIS ISSUE

The letters used to explain in which department the matter indexed appears are as follows: The Star (*) indicates an Original Article; "ab," abstract; "E," Editorial; "C," Correspondence; "Ml," Medicolegal; "ME," Medical Economics.

A. M. A. Council on Physical Therapy, Otologists' Committee on Audiometers and Hearing Aids *725
Abortion, habitual, vitamin E treatment...ab-772
Accidents, fatal, statistics, Germany.....752
Acid, adenilic, and yeast nucleic acid action on heart muscle.....751
Allyl-isopropyl-acetyl-carbamide, thrombocytopenic purpura after *725; *726; 740
Anemia, severe, from vitamin B_6 deficient diet ab-766
Angina, agranulocytic, yellow bone marrow for ab-766
Appendicitis, chronic ab-771
Arrhythmia, extrasystoles from interference of two rhythms ab-774
Asthma, allergen filter for.....751
Audiometers and hearing aids.....*723

Baker, Norman, government appeals from decision reversing conviction of.....749
Ballin Memorial Lectures.....746
Biocatalysts as proteins.....E-743
Blood, circulatory system and nucleosides...751
formation, action of splenic extract.....ab-773
sedimentation, in childhood tuberculosis..*718
Board Examinations.....761
Bone Marrow, yellow, treatment of agranulocytic angina ab-766
Bones, bleaching—dissolving tissues from skeleton—articulation of skeleton.....759
Book Notices.....762
Books Received.....Adv. page 38
Brain injury or posttraumatic neurosis.....760
electro-encephalogram in epilepsy.....E-744
tumor, mental symptoms with.....*714
Browne, Sir James Crichton, death....750; 751
Bureau of Investigation.....757
Bureau of Legal Medicine and Legislation.765
Burns, treatment with tea.....ab-772
Butesin picrate, dermatitis eczematosa due to ab-771

Cancer, Baker (Norman), reversing conviction 749
in first three decades of life.....*703; E-744
narcotics in 760
symposium, South Carolina 748
transplantable, immunity to.....ab-769
Cartilage, preservation or sterilization for grafting 760
Cataract and *di*nitrochlorobenzene.....761
incipient, use of radium on lids of eyes as cure for 760
Central Society for Chemical Research.....766
Child Neurology Research, grants available for research 749
Children, causes of lack of adaptation in older classes 751
fatigue of 751
radioscopic examination, in all rural schools 752
Comfrey root, use in rural England.....C-758
Conjunctiva, removal of silver stain.....761
Correspondence.....758
Council on Foods.....741
Council on Pharmacy and Chemistry.....740
Council on Physical Therapy.....740

Dallas Southern Clinical Society, tenth conference 748
Deaths 755
Dementia Praecox, treatment, metrazol induced convulsions *706
treatment, role of insulin in.....C-758
Dermatitis eczematosa from butesin picrate ab-771
Diabetes Mellitus, insulin-sensitive and insulin insensitive ab-768
Digitalis, dosage: use of medicine dropper.C-758
Diphtheria toxin, vitamin C effect on....ab-769
Diplopia and ptosis.....760
Disease, chronic, funds for research on.....747

Emotions, physical and emotional periodicity in women E-744
Enzymes, chemical nature.....E-743
Epilepsy: a paroxysmal cerebral dysrhythmia as demonstrated by electro-encephalogram E-744
Eye swindler attempts suicide.....749
Eyelids, ptosis and diplopia.....760

Fatigue of school children.....751
Fever, therapeutic, basal metabolism during ab-774
Fibroblasts, lymphocytes and monocytes...ab-770
Food, allergy of mouth to.....759
leukopenic index after ingesting.....761
Foreign Letters.....750

Gallbladder, surgical cases, preoperative and postoperative care *736
Gangrene in exanthematous typhus.....ab-773
Gas masks stored in nitrogen.....751
Gibbs Medal awarded to Dr. Williams for vitamin research 747
Glaucoma, hair dyes cause?.....761
Goiter, exophthalmic, iodine balance in....ab-767
International Conference 749
intrathoracic ab-771
Government Services.....750
Griffith, Ivor, new dean of Philadelphia College of Pharmacy and Science.....748

Hair dyes cause glaucoma or optic atrophy?.761
Harrison, Ross G., elected chairman of National Research Council.....749
Health activities, committees named to coordinate, Michigan 747
Hearing aids and audiometers.....*723
Heart muscle, action of yeast nucleic acid and adenilic acid on.....751
Hospital, charity racket of "Naturopathic Hospital" 748
Geisinger, graduate program at.....748
Hygiene, French Congress of.....751

Infections, virus E-742
Insulin, effect on protein metabolism.....ab-768
Iodine balance in exophthalmic goiter.....ab-767

Jaundice, therapy *732
Jefferson Medical College, faculty changes at.748

Kidney disease, protein assimilation by children with ab-769
King, Sir Frederic T., death.....750

Leprosy, International Conference.....750
Leukocytes, leukopenic index after ingesting food 761
lymphocytes, monocytes and fibroblasts..ab-770
Schilling count in tuberculosis.....*718
Libido, excessive, in woman.....761
Liver function in skin diseases.....ab-774
function tests, technic.....*737; *738; *739
Lungs, lesions (basal).....ab-771
Lymphocytes, monocytes and fibroblasts...ab-770
Lymphogranuloma venereum with inflammatory rectal strictures.....*709

Mandell, Ernest, eye swindler attempts suicide 749
Marriage laws, committee to study, Indiana.746
Marriages 754
Medical Examinations and Licensure.....761
Medical Practice Acts: drugless healers; use of title "doctor".....Ml-765
Medicine dropper use in giving digitalis ..C-758
history, graduate course on, at Johns Hopkins 746
Medicolegal Abstracts.....765
Meetings, Coming Meetings.....765
Menstruation, physical and emotional periodicity in women.....E-744
Mental Disease symptoms with brain tumor.*714
Metabolism, basal, during artificial fever..ab-774
Metrazol treatment of schizophrenia.....*706
Michigan, graduate medical education in (correction) 750
Miller, William Snow Miller Lecture.....749
Mouth, allergy to foods.....759
Mulholland, John H., appointed assistant dean at New York University.....747

Narcotics, use in paralysis agitans and cancer.760
National Research Council chairman.....749
Nature barred, Germany.....751
Nephritis, experimental embolic glomerular ab-770
Nerve, optic, atrophy, hair dyes cause?.....761
Neurology, grants available for research in child neurology 749
International Congress 749
Neurosis, anxiety states.....ab-770
posttraumatic or brain injury.....760
New and Nonofficial Remedies.....741
News 745
*di*Nitrochlorobenzene and cataracts.....761
Nitrogen, gas masks stored in.....751

Osteopaths and state registration, England..750

Paralysis agitans, narcotics in.....760
Paratyphoid B bacillus fermenting dextrotartaric acid, infection with.....ab-774
Pathologists wanted at National Institute of Health 750
Pellagra, treatment 759
treatment, nicotinic acid.....ab-766
Peptic Ulcer, surgical treatment, late results.753
Philadelphia College of Pharmacy and Science, new dean.....748
Physical Education in French schools.....752
Physiology, International Congress.....749
Pigeons as possible tetanus carriers.....ab-772
Pituitary, neurohypophysial syndrome.....754
Plague infection, California.....745
Pneumonia, serotherapy 752
treatment, rabbit serum, warning against premature use 747
Poliomyelitis, dermatophilic E-745
Polycythemia vera, gastric lavage and diet for ab-774
Protein assimilation by children with nephrosis ab-769
metabolism, insulin effect on.....ab-768
"of first importance".....E-743
Pseudo-icterus *732
Psittacosis, complement fixation test in...ab-772
Purpura, thrombocytopenic, after Sedormid *725; *726; 740

Queries and Minor Notes.....759

Radiologists, annual clinical conference, Kansas City, Mo.....747
Radium, use on lids as cure for incipient cataract 760
Rectum, inflammatory strictures with venereal lymphogranuloma *709
Rheumatic Fever, tonsillectomy effect on..ab-769
Rockefeller Foundation, funds for research on chronic disease 747
Rosacea, etiology 760
Rossiter, Perceval S., promoted to rear admiral 750

Sarcoma, transplantable, immunity to....ab-769
School of Tropical Medicine, Puerto Rico..749
Schools, open air.....751
Secretaries, county, conference of, Wisconsin.749
Sedormid, thrombocytopenic purpura after *725; *726; 740
Skin diseases, liver function in.....ab-774
Smith, Harold W., promoted to rear admiral.750
Society Proceedings.....765
Spleen, extract, action on hematopoietic organs ab-773
Stanton, Sir Thomas, death.....750
State Board Examinations.....761
State Board, new ruling, Wyoming.....749
Stomach lavage in polycythemia vera.....ab-774
Surgery, National Congress of, Italy.....753

Tetanus carriers: pigeons.....ab-772
Tetany, hypoparathyroid, A. T.-10 treatment ab-767
Therapy of Cook County Hospital.....*732
Thiamin, chemistry *727
Thrombosis, coronary, cause of death in..ab-770
coronary, residual signs a year later.....759
Thyroid, desiccated, dosage.....759
Tissues, dissolving from skeleton.....759
Tonics and Sedatives.....Adv. page 30
Tonsillectomy, effect on rheumatic infection ab-769
Tonsils, tuberculosis (primary).....ab-773
Tuberculosis in children, testing activity...*718
prevention in schools.....752
sanatorium, first one in Florida.....745
sanatorium (state), new one started, Pennsylvania 748
Typhus, exanthematous, gangrene in.....ab-773

University of California Publication in Pharmacology 745
Urethra, posterior, obstruction.....ab-773
Urinary Tract, calculi, late results of surgical treatment 754
Urine, therapeutic use for wounds.....C-758

Venereal Disease control, federal aid for, Kansas 746
Virus infections E-742
Vitamin B_1, chemistry of thiamin.....*727
B_6 deficient diet, severe anemia from..ab-766
C effect on diphtheria toxin.....ab-769
deficiency, public lecture on, Maryland....746
E treatment of habitual abortion.....ab-772
Gibbs Medal awarded to Dr. Williams for research on 747

Workmen's Compensation Acts: insanity; when a compensable injury.....Ml-765
Wound healing, use of urine and also comfrey root C-758

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CARCINOMA IN THE FIRST THREE DECADES OF LIFE

NORMAN HALL, M.D.
AND
JAMES W. BAGBY, M.D.
ST. LOUIS

The old concept of cancer as a disease highly selective of the latter span of life is undoubtedly a factor that militates to no small degree against proper recognition of this disease. Furthermore the seeming tendency of cancer to manifest itself to an increasing degree during the earlier decades of life is a fact calling for more emphasis than is laid on it in current literature. For these reasons we have made this study of the material at the Barnard Free Skin and Cancer Hospital, where, since 1908, there have been 134 patients between 8½ and 31 years of age in whom the diagnosis of cancer was confirmed by microscopic examination.

This paper treats of carcinoma alone in patients of 30 years or younger. Sarcoma and other malignant conditions have not been included. The more one sees of cancer and studies it microscopically, the more is one convinced that occasional mistakes are made in the diagnosis of cancer. We feel that much confusion has arisen regarding end results and statistics in the incidence and treatment of cancer, owing to the fact that data are often given in instances of unproved (by microscopic examination) carcinoma. To obviate any such confusion and doubt, we have in this paper divided our cases into two groups:

1. "Proved cases," those in which a positive microscopic diagnosis was made.
2. "Clinical cases," those in which there was no report of microscopic examination (in many of which treatment had been by radium or cautery).

We feel sure that all, or practically all, of the cases placed in the second group (clinical cases) were carcinoma. The history and manifestations point to cancer, many of the patients having had tumors removed previously with subsequent recurrence and many were later reported "dead of cancer." All these cases were diagnosed cancer by staff members who have had wide experience in this line of work. However, we feel, as already stated, that only cases determined by a microscopic report should be used in a statistical study; therefore in this paper, although we give a list of the "clinical cases," all statistics are based on the "proved cases." Wherever we mention "duration" or "duration of symptoms" we refer to the period from the time when the patient noticed the first symptom until he or she reported to the clinic.

Table 1 shows the occurrence of carcinoma in our cases (both proved and clinical) as well as the sex ratio. It will be seen that of the 134 cases which were proved by microscopic examination twenty-nine (21.6 per cent) occurred in males while 105 (78.4 per cent) were in females.

These 134 cases can be presented in detail statistically in most suitable fashion by classifying them according to the various organs, or groups of organs, involved in the disease as listed in table 1 under "site."

Table 2 shows that of the eleven patients with carcinoma confirmed microscopically the youngest was 22 years of age (there being three patients this age). Of those with "proved cancer" seven were males and four females. The duration, up to the time of admission to the hospital, varied from one month to twelve years, the average being two years.

Of the eleven patients, one died of cancer in less than one year (carcinoma of the ear with metastases to the parotid region) and one died following an appendectomy one year after treatment for cancer. Two had no recurrence for periods of under one and two years respectively. One had no recurrence after nine years and one had none after eleven years. Five of the cases have not been traced.

It will be seen from table 3 that, of the proved cases, the youngest patient with carcinoma of the nose was 22 years of age. Of the five patients four were males, one female. The duration of the disease, up to the time of admission to the hospital, varied from five weeks to eight years, the average being a little over two and one-half years.

Table 4 shows two proved cases of carcinoma of the upper lip, the younger patient being 25 years of age. The duration of these two cases was two and one-half and one and one-half years.

From examining table 5 it will be seen that of the ten proved cases, all occurring in males, the youngest patient was 19 years of age. The shortest duration (from the time the patient first noticed the lesion until he applied to the clinic) was two months. The longest duration was four years; the average for the ten patients was eighteen months. Seven of the patients had radical lip operations (Stewart operation or a modification). One had a V excision. One was treated by radium alone; he received several applications and had a rather severe reaction with enlargement of the submaxillary nodes. A suprahyoid dissection was advised, but he did not consent. One patient was not treated at the Barnard Hospital. Only one of the seven patients who had lymph nodes removed had metastases. He was first treated by radium and then underwent a radical lip operation, following which he has been clin-

From the Surgical and Dermatological Services of the Barnard Free Skin and Cancer Hospital.

ically cured for five years. Of the nine patients treated, three have been treated for a period of less than one year, three had no recurrence after a period of three years, one had no recurrence after five years, while one has gone for a period of eleven years without recurrence. One patient has not been traced.

TABLE 1.—*Occurrence of Carcinoma with Sex Ratio (Proved and Clinical Cases)*

Site	Proved Cases (Microscopic Diagnosis) No. of Cases	Males	Females	Clinical Cases (No Microscopic Diagnosis) No. of Cases	Males	Females	Total Proved and Clinical
Face (other than nose or lips)	11	7	4	17	13	4	28
Nose	5	4	1	8	4	4	13
Upper lip	2	1	1	1	1	0	3
Lower lip	10	10	0	6	6	0	16
Mouth	4	1	3	2	2	0	6
Gastro-intestinal tract	7	3	4	1	1	0	8
Breast	22	0	22	9	0	9	31
Extremities	5	1	4	0	0	0	5
Miscellaneous	2	0	2	0	0	0	2
Penis	0	0	0	1	1	0	1
Xeroderma pigmentosum with carcinomatous changes	3	2	1	0	0	0	3
Gynecologic cancer (other than cervix)	6	0	6	1	0	1	7
Cervix uteri	57	0	57	26	0	26	83
Total	134	29	105	72	28	44	206

Of the cases of carcinoma of the mouth the shortest duration, from first symptoms to admission, was two and one-half months, the longest two years. The 21 year old woman with carcinoma of the tongue died three weeks after she was first seen. The other patient with carcinoma of the tongue died fourteen months after first applying for treatment. The tongue was treated with radium and she had a bilateral dissection of the neck for metastases. The boy with carcinoma of the throat had cervical metastases on admission and died within two and one-half months. The 24 year old woman with nasopharyngeal carcinoma now has extensive metastases in spite of roentgen therapy and dissection of the neck.

The 28 year old man with adenocarcinoma (grade 2) of the stomach had a partial gastric resection elsewhere, was treated here by roentgen rays and died within six months of the operation. The carcinoma of the ampulla of Vater was of three months' duration and the patient died within four months after first applying for treatment. The woman with carcinoma of the colon went elsewhere and it has been impossible to get a follow-up. Of the three rectal cases, durations were given as one month, five months and one year. One patient died within three months, one died postoperatively and one has had an artificial anus for six months. The latter has had a large dose of radium and roentgen rays, is inoperable and is doing poorly. The 30 year old woman with squamous cell carcinoma (grade 3) of the anus was operated on one and one-half years ago, and so far there are no signs of metastases.

TABLE 2.—*Carcinoma of the Face*

Site	Age	Sex	Tumor Type
Eleven Proved Cases			
Outer canthus	30	♂	Squamous cell, grade 2
Eyelid	28	♀	Basosquamous
Multiple	22	♀	Basal cell
Skin of parotid region	25	♂	Squamous cell, grade 3
Cheek	22	♂	Squamous cell
	30	♀	Squamous cell
Temple	30	♂	Squamous cell, grade 1
	26	♂	Melanocarcinoma
Ear	22	♀	Squamous cell
Skin of neck	30	♂	Basal cell
Face	28	♂	Squamous cell
Seventeen Clinical Cases			
Cheek (3)	22 (2)		♂ (2)
	29		♂
Forehead (2)	18		♂
	29		♂
Face (11)	22 (2)		♂, ♀
	25		♂
	27		♂
	29 (4)		♂ (4)
	30 (2)		♀ (2)
	30		♂
Skin, chin	29		♀

TABLE 3.—*Carcinoma of the Nose*

Five Proved Cases Age	Sex	Tumor Type	Eight Clinical Cases Age	Sex
22	♂	Squamous cell, grade 1	21	♀
25	♀	Basal cell	22	♀
27	♂	Basal cell	24	♂
27	♂	Hair follicle carcinoma	26	♂
30	♂	Basosquamous	30 (4)	♂ (2), ♀ (2)

TABLE 4.—*Carcinoma of Upper Lip*

Two Proved Cases Age	Sex	Tumor Type	One Clinical Case Age	Sex
25	♀	Basal cell	24	♂
29	♂	Squamous cell		

TABLE 5.—*Carcinoma of the Lower Lip*

Ten Proved Cases Age	Sex	Tumor Type	Six Clinical Cases Age	Sex
19	♂	Squamous cell, grade 2	24	♂
24	♂	Squamous cell	24	♂
24	♂	Squamous cell	24	♂
24	♂	Squamous cell, grade 1	26	♂
24	♂	Squamous cell, grade 2	29	♂
25	♂	Squamous cell	30	♂
26	♂	Squamous cell		
27	♂	Squamous cell, grade 2		
27	♂	Squamous cell, grade 3		
28	♂	Squamous cell		

About six months ago a bilateral inguinal gland dissection was done. The nodes were hyperplastic but no metastases were found.

Of the patients with proved carcinoma of the breast the youngest was 22 years of age (two patients). Three of the twenty-two patients were single and at least three others had never been pregnant. Four of the patients had had previous operations elsewhere, with recurrence. One patient had been "watched" by a physician for ten months. Four of the twenty-two patients were Negresses. Seven patients gave a history of duration, from first noticing symptoms to entering the clinic, of one month or less, six patients of from one to six months, four of from seven months to one year, three patients of from one to two years, while two were indefinite. Sixteen of the twenty-two patients had radical operation (of which eight had axillary node metastases at the time of operation). Three had roentgen therapy only; two went elsewhere for treatment. One was not treated (had previous operation). Of the twenty-two patients with proved carcinoma, nine are known to be living, five are dead, six are untraced

(one followed for five months, two for one year) and two were operated on elsewhere. Of the nine known living patients, five have been operated on for less than two years, one has survived three years, one four years, one six years and one seven years. It is interesting to note that the patients who have gone six and seven years without recurrence both had axillary metastases at the time of operation and surely would have been dead long before this if a radical operation had not been done.

The duration of the disease in persons with carcinoma of the extremities varied from one year to four years, the average being about two years. One patient had no recurrence in more than two years, one none in more than four years, while three cannot be traced.

MISCELLANEOUS

Proved Case.—A woman, aged 26, with adenocarcinoma of the left supraclavicular region (Virchow's node), primary lesion unknown, of two months' duration, died within three months.

Clinical Case.—A man, aged 30, had had an operation elsewhere for carcinoma of the penis of one year's duration. He was told that he had cancer but sections were not seen at this hospital. He died elsewhere, supposedly of cancer, within five months.

SKIN

There were twenty-six cases of carcinoma of the skin, confirmed microscopically, in patients 30 years of age or under. Twenty-two of these cases have already been listed under "face" or "extremities." Of the remaining four, one woman, aged 27, had a basal cell carcinoma of the skin of the back, and three patients had xeroderma pigmentosum with carcinomatous changes, one being an 8½ year old girl who had a grade 1 squamous cell carcinoma; the other two were boys aged 9 and 18 years, both with squamous cell carcinoma.

The three patients with carcinoma of the ovary had never been pregnant. The 15 and 17 year old girls were unmarried. The 17 year old girl was a Negress. The duration of symptoms in these cases (ovary) was six weeks, five months and nine months. The duration of the vaginal cases was indefinite. One of the patients with carcinoma of the vagina was not treated here (biopsy only); the other two died within six and seven months. The patients with carcinoma of the ovary died within two, six and fourteen months.

The youngest patient was 20 years of age. Four patients gave a history of duration of one month or less, thirty-four patients of six months or less, sixteen patients of from six to twelve months. The average duration for the group was slightly less than six months. Two patients were not treated at the clinic (biopsy only), three have not been traced, twenty-one were alive when last seen, or heard from, while thirty-

TABLE 6.—*Carcinoma of the Mouth*

Four Proved Cases

Site	Sex	Age	Tumor Type
Tongue	♀	21	Squamous cell
Tongue	♀	24	Squamous cell, grade 3
Throat	♂	21	Squamous cell, grade 4
Nasopharynx	♀	24	Squamous cell, grade 2

Two Clinical Cases

Site	Age	Sex	Comment
Upper jaw	28	♂	Operation elsewhere
Palate	27	♂	Inoperable, previous operation elsewhere

TABLE 7.—*Carcinoma of the Gastro-Intestinal Tract*

Seven Proved Cases

Site	Age	Sex	Tumor Type
Stomach	28	♂	Adenocarcinoma, grade 2
Ampulla of Vater	26	♂	Adenocarcinoma, grade 3
Colon	27	♀	Adenocarcinoma
Rectum	25	♂	Adenocarcinoma, grade 4
Rectum	28	♀	Adenocarcinoma, grade 1
Rectum	30	♀	Adenocarcinoma
Anus	30	♀	Squamous cell, grade 3

One Clinical Case

Site	Age	Sex	Comment
Rectum	30	♂	Had colostomy done elsewhere

TABLE 8.—*Carcinoma of the Breast*

Twenty-Two Proved Cases

Patients	Age, Years	Sex	Tumor Type	
4	22-25	All females	Adenocarcinoma	
			Not graded	14
18	26-30	All females	Grade 3	6
			Grade 4	2

One patient with adenocarcinoma, grade 3, was carcinoma en cuirasse

Nine Clinical Cases

3	22-24	All had "lumps" removed which recurred (1 twice)
6	25-30	Two had lumps removed which had recurred

TABLE 9.—*Carcinoma of the Extremities (Five Proved Cases)*

Site	Age	Sex	Tumor Type
Arm	19	♀	Adenocarcinoma
Arm	80	♀	Melanocarcinoma
Thigh	20	♀	Squamous cell
Thumb	24	♂	Squamous cell, grade 2
Elbow (skin)	28	♀	Cystic basal cell

TABLE 10.—*Carcinoma of the Female Genital Tract Other Than Cervix*

Six Proved Cases

Site	Age	Tumor Type
Vaginal wall	26	Squamous cell
Vagina	27	Squamous cell
Vulva	26	Squamous cell
Ovary	15	Colloid carcinoma
Ovary	17	Adenocarcinoma, grade 3
Ovary	26	Cystic adenoma; carcinomatous changes

One Clinical Case

Site	Age	Comment
Ovary	25	Patient had several previous operations; treated here with roentgen rays, lived almost 5 years

TABLE 11.—*Carcinoma of the Cervix Uteri*

Fifty-Seven Proved Cases

Patients	Age	Tumor Type	
14	20-25	Squamous cell, grade 1	1
		Squamous cell, grade 2	13
43	26-30	Squamous cell, grade 3	19
		Squamous cell, grade 4	4
		Adenocarcinoma, grade 1	1
		Adenocarcinoma, grade 2	1
		Not graded (squamous cell)	18

Twenty-Six Clinical Cases

13 patients were dead within 14 months
18 not treated or untraced

one are dead. Of the living patients eleven were alive at one year, four at from one to two years, one at from two to three years, three at four years, one at from four to five years and one over five years.

COMMENT

The youngest patient with carcinoma in our series was 8½ years old (xeroderma pigmentosum, with carcinomatous changes). The youngest patient with carcinoma of the lip was 19 years of age, of the breast 22 years (two patients), of the ovary 15 years, of the cervix 20 years, and of multiple basal cell carcinoma 22 years.

For the past five years, in this clinic, excluding the female genital tract and breast, 1.7 per cent of the cancer cases with microscopic diagnosis occurred in persons 30 years of age or younger. For the same time 7.4 per cent of the patients with proved carcinoma of the cervix were in the first three decades of life. Four and three-tenths per cent of the breast cancers occurred in the same age period.

Carcinoma of the cervix and breast in persons 30 years of age or younger has increased in a greater ratio at this clinic for the past five years as compared to the previous five years than the same condition in older women.

Carcinoma of the cervix, mouth and breast (to a lesser degree) is more malignant, with a poorer prognosis, in young persons than the same condition in older patients.

The grading of the microscopic sections, the symptoms and duration are about the same in persons of 30 years or younger as in older persons.

Sarcoma is generally considered to be more frequent in young persons than in older ones. However, at this clinic, regarding the actual number of cases, carcinoma is more frequent in the first three decades of life than sarcoma.

CONCLUSIONS

One hundred and thirty-four cases of carcinoma occurring in persons of 30 years of age or younger were confirmed by microscopic examination.

The main purpose of this paper is to reemphasize the all important fact that carcinoma can and does occur in persons 30 years and younger in practically all anatomic locations. The age of the patient must not influence one in procrastination and "watchful waiting." The results of treatment in young persons, as in older ones, depend on early diagnosis and adequate treatment.

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Obsolete Spare Parts.—Man is a made-over animal. In the course of evolution, his ancestors have functioned as arboreal pronogrades and brachiators or arm progressing tree dwellers—not to mention more remote stages involving other changes of habitat, posture and mode of locomotion. This protean history has necessitated repeated patching and reconstruction of a more or less pliable and long suffering organism. The bony framework has been warped and cramped and stretched in one part or another, in accordance with variations in the stresses and strains put upon it by different postures and by changes in body bulk. Joints devised for mobility have been readapted for stability. Muscles have had violence done to their origins and insertions and have suffered enormous inequalities in the distribution of labor. Viscera have been pushed about hither and yon, hitched up, let down, reversed and inverted. In making a new machine out of an old one, plenty of obsolete spare parts have been left to rattle around inside.—Hooton, E. A.: Apes, Men, and Morons, New York, G. P. Putnam's Sons, 1937, page 243.

THE TREATMENT OF SCHIZOPHRENIA WITH METRAZOL BY THE PRODUCTION OF CONVULSIONS

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CHICAGO
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Putting into practice his hypothesis that schizophrenia and epilepsy are biologically antagonistic entities, Meduna [1] attempted to bring about a remission of schizophrenia by the production of epileptiform seizures. He began his experiments by using camphor in oil but later used pentamethylenetetrazol (metrazol) because of its greater reliability as a convulsant drug. He treated with this method 110 schizophrenic patients, of whom fifty-four had a remission. This is a percentage of about 50 per cent, which exceeds the percentage reported for spontaneous remissions from almost all clinics. Moreover, when the remissions are classified according to duration of the disease, the percentage rises to 90 per cent, for patients who were ill less than one year. Regardless of the validity of Meduna's theory that epilepsy and schizophrenia are biologically antagonistic disease entities, the high percentage of therapeutic results which he reported merited further investigation. His results have been corroborated by Wahlmann,[2] von Angyal and Gyárfás,[3] Friedman [4] and others. Gullotta [5] was unable to confirm them, but he produced only eight convulsive seizures in each of his ten schizophrenic patients.

We began the use of metrazol in the treatment of dementia praecox [6] at the Elgin State Hospital March 1, 1937.

USE OF METRAZOL AS A CONVULSANT

The patient is given a thorough physical examination to rule out infectious process, pulmonary disease or cardiovascular disorders, which are contraindications.

The treatment is given in the morning when the patient's stomach is empty. The dose is the smallest amount of the drug that will produce a typical convulsive seizure. There is no relationship between body weight and the amount of drug necessary to produce a convulsive reaction. Our first dose ranged from 2 to 5 cc. of a 10 per cent solution. As a rule we administered 1 cc. for about each 30 pounds (13.6 Kg.) of body weight but not over 5 cc. for the first dose. This dose usually produced a convulsion. When the convulsive dose was reached, it was maintained until we failed to get a reaction. In such cases the treatment was repeated the next day, the dose being increased by 1 cc. For patients with a longer duration of the

Read before the Chicago Neurological Society, Oct. 21, 1937.
Dr. C. F. Read gave helpful suggestions during the course of the work.
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1. de Meduna, L.: New Methods of Medical Treatment of Schizophrenia, Arch. Neurol. & Psychiat. **35**: 361 (Feb.) 1936; Die Konvulsionstherapie der Schizophrenie, Psychiat.-neurol. Wchnschr. **37**: 317 (July 6) 1935; Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenie: Campher-und Cardiazolkrämpfe, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**: 235-262, 1935.
2. Wahlmann: Vorläufige Mitteilung über Konvulsionstherapie der Psychosen, Psychiat.-neurol. Wchnschr. **38**: 78-79 (Feb. 15) 1936.
3. von Angyal, L., and Gyárfás, K.: Ueber die Cardiazol-Krampfbehandlung der Schizophrenie, Arch. f. Psychiat. **106**: 1, 1936.
4. Friedman, E.: Personal communication to the authors.
5. Gullotta, S.: La cura della schizofrenia con la provocazione di convulsioni epilettiche, Riv. sper. di freniat. **60**: 510 (Dec. 31) 1936.
6. We had had no experience with metrazol in the treatment of other conditions, such as postanesthetic collapse or barbiturate poisoning.

psychosis the dose of the drug had to be increased more often than for others. The treatment was administered two or three times a week.

When the dose is insufficient to produce a complete convulsion, a minimal reaction consisting of mental confusion and a few myoclonic movements occurs. With a still smaller dose there is no reaction except pallor, cough and an anxious facial expression.

The treatment is continued until the patient shows a remission. The patient is observed from two weeks to a month before parole is recommended. If during this observation period he relapses, the treatment is resumed until improvement is again noted. Two patients relapsed after being home for two months. One had had ten convulsions. He was returned to the hospital and treatment reinstituted, and after thirteen more convulsions he again appeared in good remission and was returned to his home. The other patient has shown no further response to treatment.

As a rule from twenty-five to thirty injections are given. However, if a patient shows some signs of improvement the injections are continued until there is no further evidence of improvement.

Injury to the tongue is prevented by placing a soft rubber wedge between the teeth during the tonic phase when the mouth is open. There were no fatalities in our cases. However, minor complications are at times encountered, such as dislocation of the mandible and dislocation of the head of the humerus. These dislocations were reduced and their recurrence prevented by supporting the parts involved.

PATTERN OF THE CONVULSIONS

With the aid of cinematographic and kymographic tracings (fig. 1) we observed the following series of events in the motor pattern of the convulsion produced by metrazol.

From two to five seconds after the intravenous administration of metrazol the patient coughs, and five seconds later marked pallor of the face occurs. From three to ten seconds after the injection an intense blepharospasm occurs and the facial expression is a mixture of bewilderment and fear. Five seconds later myoclonic convulsive movements begin in the face, shoulders and arms, sometimes only on one side. A well marked rhythmic clonic phase develops, as shown clearly by the tracings (fig. 1). After about fifteen seconds a tonic phase ensues. The head is retracted and the back arched. The eyeballs may move upward or to either side or remain in the original plane. The arms and legs are tetanically contracted in extension. The wrists and fingers are flexed, the position of the thumb frequently being between the index and the middle finger. Sometimes before the opisthotonos there is a flexion of the thighs, legs and feet, with the large toes in the Babinski position. This is followed by an extension of the lower extremities. Frequently there is an adductor spasm, with the legs in a scissor-like position. These positions of the body may change during the tonic phase; the knees may be flexed on one side and extended on the other. There may be a rotation of the pelvis to one or the other side, with flexion of the thighs and legs, followed by an extension. Similarly, the upper extremities may assume various postures.

The tonic phase lasts from five to thirty seconds and is followed by another clonic phase. The first clonic movements break through in the fingers and spread to involve the entire body. Such rhythmic clonic movements are seen while the extremities are still held in tonic extension. The clonic movements are at first rapid, gradually become less frequent with increasing amplitude and cease after about twenty-five seconds. During this stage ejaculation may occur. Urination is observed after relaxation. During the tonic phase and the succeeding clonic one, there is a period of apnea, with marked cyanosis. After a few seconds the patient resumes breathing. A pilomotor reaction is present during the toxic phase and gradually disappears during the apneic period. Sometimes the lower extremities and not infrequently the upper extremities are rigidly extended after the second clonic phase. After the convulsion the patient frequently is drowsy and may fall asleep. About one minute after the last clonic phase a period of restlessness may occur. The patient may thrash his arms about, or there may be a definite pattern of movements, such as rolling of the body to the side. About five minutes after the injection the patient's attention may be attracted by verbal stimuli. As a rule each individual has his own constant motor pattern. The patient may show some motor restlessness immediately before the first clonic phase, such as flapping his arms as in "wing beating," brushing his face or alternately raising or lowering his legs.

In the majority of cases there is a short period of areflexia soon after the convulsion, which is followed

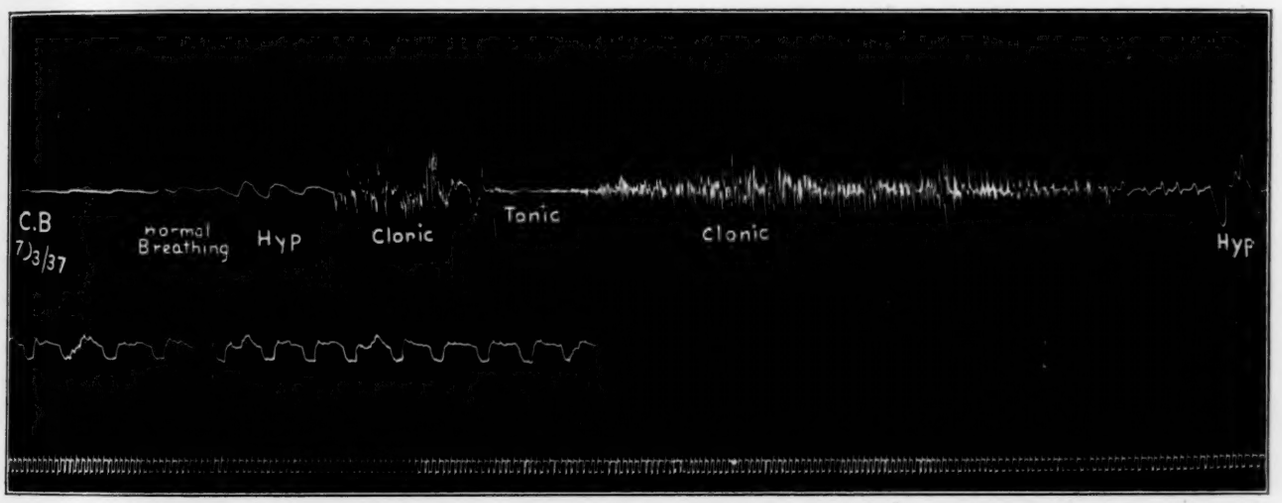

Fig. 1.—Motor pattern of the metrazol convulsion, showing the clonic-tonic-clonic sequence.

in a few seconds by increased deep reflexes, sustained ankle clonus and the Babinski sign. Usually there is a short period of confusion after the seizure. In some patients the confusion may last several hours. The patient has total amnesia for the phenomena, recalling only the injection and a feeling of anxiety. One patient counted to thirty after the injection but after the reaction stated that he recalled counting only to twelve.

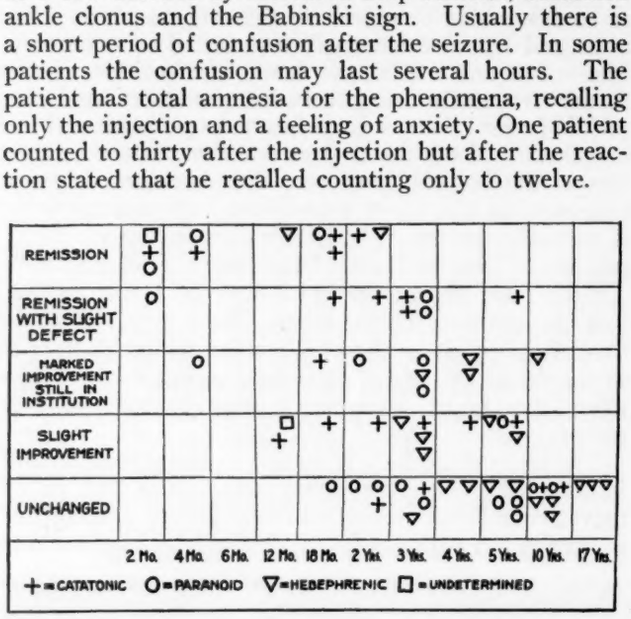
REMISSION
REMISSION WITH SLIGHT DEFECT
MARKED IMPROVEMENT STILL IN INSTITUTION
SLIGHT IMPROVEMENT
UNCHANGED
2 Mo. 4 Mo. 6 Mo. 12 Mo. 18 Mo. 2 Yrs. 3 Yrs. 4 Yrs. 5 Yrs. 10 Yrs. 17 Yrs.
+ = CATATONIC O = PARANOID ▽ = HEBEPHRENIC □ = UNDETERMINED

Fig. 2.—Results of treatment in relation to the duration of the psychosis.

The pupils are dilated during the convulsion and do not react to light. In some cases there is profuse perspiration after the convulsion. The blood pressure rises from 20 to 60 mm. of mercury during the seizure and drops to its normal level in from ten to thirty minutes.

We have described the motor pattern of the convulsion produced by metrazol in some detail because it differs from that produced by other convulsant drugs. The metrazol convulsive pattern follows a clonic-tonic-clonic sequence and indicates a complete and intensive reaction of the central nervous system. Pollock [7] and his co-workers have observed in animal experiments with various convulsant drugs that this clonic-tonic-clonic sequence occurs most consistently after the injection of metrazol. Camphor monobromide, thujone, picrotoxin and insulin produce only clonic convulsions or, occasionally, tonic-clonic convulsions. At times a clonic-tonic-clonic sequence is observed with drugs other than metrazol, but only if lethal or almost lethal doses are employed.

ANALYSIS OF SIXTY-SIX CASES

We classified the therapeutic results in five groups: (1) complete remission, (2) remission with defect, (3) marked improvement, (4) slight improvement and (5) no change.

A patient is considered to be in a complete remission if he has returned to his prepsychotic level as determined by the history and if he has resumed his previous employment, shows no defect in ideation and behavior and has insight. If he lacks insight or shows other psychic symptoms but is able to adjust at home and resume his work, the result is classified as remission with defect. The patient with marked improvement remains in the institution and, although on a much higher level than he was prior to treatment, still requires supervision. Slight improvement indicates that some symptoms have disappeared but that the patient still has a preponderance of psychotic symptoms. One of the first objective signs of improvement in most patients is the change in affect or mood. The patient appears to relax and is more agreeable and sociable toward other patients and the hospital personnel, spontaneously helping with the hall work and even requesting to be industrially employed about the institution. Soon he becomes more interested in the environment and asks for his people, often spontaneously writing to them. It is obvious that psychotherapy has an important part in his progress at this point.

Among the sixty-six patients in our group, all types of dementia praecox except the simple were represented. The duration of the psychosis ranged from two months to seventeen years, in the majority of cases being over two years. In table 1 is given an analysis of the effect of treatment with relation to the duration of the psychosis. For example, in five of the seven cases in which the duration of the disease was six months or less there was a complete remission and in one a remission with a slight defect. One patient is markedly improved.

No patient who had had the disease more than two years had a complete remission. However, a remission with a slight defect could be obtained. The percentage of remissions drops very rapidly, so that after a duration of three years no remission is to be anticipated.

Table 2 is an analysis of the effect of therapy in relation to the various types of dementia praecox. Our results as given in this table indicate that the best results are obtained in treating the early types of catatonic and paranoid dementia praecox.

Figure 2 indicates clearly the absence of complete remissions when the patient had been ill over two years and the fact that no patient who had been ill under one year failed to show some response to treatment.

The question arises as to whether there is a relationship between the number of treatments and the duration of the psychosis. By observing patients with a remission we have seen that the number of injections necessary to produce a remission increases with the duration of the psychosis (fig. 3). For patients ill eighteen months or under, the average number of injections was ten and three-tenths and for those ill over eighteen months twenty-five and seven-tenths.

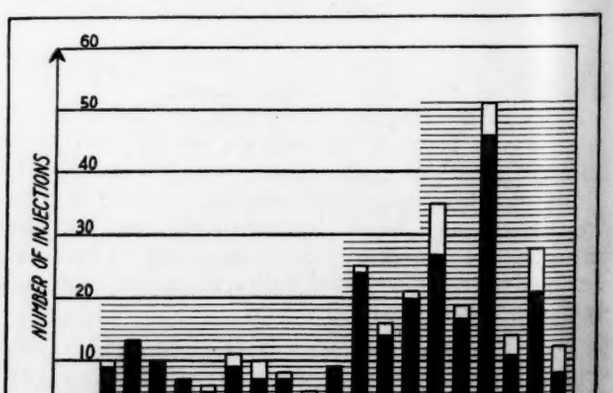

Fig. 3.—The number of treatments preceding a remission related to the duration of the psychosis.

Many patients gain weight during treatment. We have not observed any critical changes in the cellular constituents of the blood, nor were there any noteworthy changes in the cholesterol, sugar, calcium and acid-soluble phosphorus contents of the blood before, during and at varying intervals after the seizure.

7. Pollock, L. J.; Finkelman, Isidore; Sherman, I. C., and Steinberg, D. L.: The Motor Pattern of Convulsions Produced by Various Drugs, read before the Central Neuropsychiatric Association Oct. 9, 1937.

SUMMARY AND CONCLUSIONS

The convulsive treatment with metrazol is of value in the treatment of patients with dementia praecox, particularly when the duration is not more than two years. The procedure does not require extensive arrangements and can be carried out in any hospital. Results may be expected fairly early.

The convulsive seizure produces many changes in the organism, such as anoxemia followed by increased oxygenation, an increase in the supply of blood to the brain and an increase in the activity of the muscles with all the chemical changes accompanying such activity. All or some of these factors may be responsible for the remission produced in the schizophrenia. The problem still remains, however, of how physical changes in the body cause psychic symptoms to appear and disappear.

We treated sixty-six patients with dementia praecox by the administration of metrazol. The results were analyzed according to the duration and the type of dementia praecox. We found that 85 per cent of the patients whose symptoms were less than six months in duration had a remission. The rate of remission is almost inversely proportional to the duration of the psychosis. If the psychosis has lasted more than three years the anticipation of a remission is slight. Patients who showed a remission although their psychosis was over eighteen months in duration required larger doses of the convulsant drug and a greater number of convulsions. The type of dementia praecox that shows the greatest tendency to remit with this therapy is the catatonic, followed closely by the paranoid. Contraindications to this therapy are acute infectious diseases, pulmonary disease and cardiovascular disorders. We had no fatalities, and the only complications encountered were dislocation of the mandible and dislocation of the humerus.

303 East Chicago Avenue.

TABLE 1.—*The Effect of Treatment with Relation to the Duration of the Disease*

Duration, Months	Number of Patients	Remission	Remission with Slight Defect	Marked Improvement; Patient Still in Institution	Slight Improvement	Percentage at Home
1-6	7	5	1	1	0	85.0
7-12	3	1	0	0	2	33.0
13-18	7	3	1	1	1	57.0
19-24	8	2	1	1	1	37.5
25-36	15	0	4	3	4	26.6
37-48	5	0	0	2	1	0
49-60	10	0	1	0	4	0
60 and over	11	0	0	1	0	0

TABLE 2.—*The Percentage of Patients at Home and Improved as Related to the Diagnosis and the Duration*

	Number of Patients	Duration, Months	Improved	At Home
Catatonic	12	1-24	83%	58%
	9	25-204	66%	33%
Paranoid	9	1-24	66%	44%
	12	25-204	41%	17%
Hebephrenic	2	1-24	100%	100%
	20	25-204	45%	0
Undetermined	2	1-24 25-204	50%	50%

INFLAMMATORY STRICTURES OF THE RECTUM ASSOCIATED WITH VENEREAL LYMPHOGRANULOMA

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SAN FRANCISCO

Although the clinical picture associated with that form of venereal lymphogranuloma occurring mainly in males and resulting in inguinal adenitis has been known since 1913,[1] it was not until 1927 that Frei [2] suggested that certain types of benign rectal stricture of unknown cause, together with many strictures thought to be due to tuberculosis, gonorrhea and syphilis, might be manifestations of this same disease. Frei and Koppel [3] then substantiated this assumption by demonstrating a positive cutaneous reaction to intradermal injections of diluted pus known to contain the virus of venereal lymphogranuloma in a number of their cases of inflammatory stricture of the rectum. Since that time a number of other reports have appeared in the literature confirming their results.

ETIOLOGY

Certainly all benign strictures of the rectum cannot be attributed to venereal lymphogranuloma; however, many of the etiologic theories suggested in the past are entirely unconvincing. A comprehensive review of the literature leaves little doubt that most of the early investigators regarded inflammatory strictures of the rectum as a late manifestation of syphilis, although it was noted that the lesions did not respond to the ordinary antisyphilitic treatment. Many of the later investigators turned to tuberculosis, amebic dysentery, gonorrhea and chancroid as the etiologic factors concerned. It is logical that syphilis should have been considered by most observers as the outstanding etiologic basis of rectal stricture. A large percentage of patients suffering with the malady have syphilis. The reason for this is obvious in view of the venereal nature of venereal lymphogranuloma. The Wassermann reaction has been used as a proof of syphilis as a causative agent. One author, Kallet,[4] reported a positive Wassermann reaction in as many as 38 per cent of a large series of patients with rectal stricture. On the other hand, no strictures were encountered by Schede [5] in 17,810 men treated for syphilis and only sixteen in 18,780 syphilitic women; this makes the syphilitic origin quite improbable. It is also true that the histologic changes often attributed to syphilis are considered by more recent authors to be nonspecific inflammatory reactions. The histologic changes which have been claimed as "typically syphilitic" are, as mentioned by Stannus,[6] the same changes which the tuberculosis enthusiasts recognize as essentially "tuberculous." Considering the enormous number of people suffering from tuberculosis who never show signs or

From the Stanford University Surgical Service, San Francisco Hospital, unit of the San Francisco Department of Public Health.

The Surgical Service of the University of California at the San Francisco Hospital permitted examination and study of many of their patients.

1. Durand, M.; Nicolas, J., and Favre, M.: Société de chirurgie de Lyon, meeting of Feb. 20, 1913; Lyon méd. **121**: 64, 1913; Lyon chir. **9**: 561, 1913.
2. Frei, Wilhelm: Der gegenwärtige Stand der Kenntnisse von der Elephantiasis genito-anorectalis (Esthiomene, entzündliche Rektumstriktur), Deutsche med. Wchnschr. **58**: 1964 (Dec. 9) 1932.
3. Frei, Wilhelm, and Koppel, Alice: Ulcus Vulvae, Esthiomene, Klin. Wchnschr. **7**: 2331 (Dec. 2) 1928.
4. Kallet, H. J.: Proctitis Obliterans, J. Michigan M. Soc. **2**: 432, 1921.
5. Schede, Max: Ueber die Resection des Mastdarmes bei den Stricturirenden Geschwuren desselben, Arch. f. klin. Chir. **1**: 835, 1895.
6. Stannus, Hugh S.: A Sixth Venereal Disease, Baltimore, William Wood & Co., 1933.

symptoms of rectal stricture, it would seem improbable that tuberculosis is a frequent cause of stricture.

Finkelstein [7] has observed not a single case of true inflammatory stricture of the rectum in an enormous number of cases of amebic dysentery. The occurrence of Endamoeba histolytica in cases of rectal stricture of various types probably is no higher than its incidence in association with many other diseases. The infrequency of development of stricture after gonorrheal proctitis speaks against this disease as an etiologic factor. Many unconvincing reports appear in the literature. It would seem from our present knowledge of the pathogenesis of venereal lymphogranuloma in many cases of rectal stricture that, even in the presence of gonococci, there probably was a coincident infection with the virus of venereal lymphogranuloma. Stannus [6] stated:

> Because the patient has had gonorrhea, chancroid or syphilis, or all of these diseases, there is no prima facie case for supposing they are etiological factors. Gummatous or tuberculous ulceration of the rectum may produce stricture of the rectum, but they do not produce "inflammatory stricture of the rectum." When these diseases and gonorrhea, etc., have been put forward as causes, the essential points in the nature of the condition appear to have been lost sight of. The pathogenesis of this type of stricture cannot be explained on such a basis. . . .

The frequent finding of a positive Frei test in patients suffering with inflammatory stricture of the rectum is strong evidence that this disease is the real etiologic factor in the majority of cases.

CLINICAL PICTURE

The clinical picture of the disease in the rectum, at least in the advanced stages, is unmistakable. There is a progressive history of bloody mucous discharge from the rectum, pruritus and tenesmus, with intermittent periods of marked constipation and in many cases acute obstruction. In most series the disease is reported to occur far more commonly in women than in men and in this country most frequently in Negroes. This has not been the experience of my co-workers and me at the San Francisco Hospital. In our series of seventy-eight patients, sixty were men and eighteen were women, and of these only twelve were Negroes. The stricture itself usually is one of three fairly distinct types, though occasionally combinations of these occur. The first type consists of an annular diaphragm of fibrous consistency occurring most commonly from 1 to 6 cm. above the anocutaneous margin. A small aperture usually remains in the central portion of the diaphragm, through which the mucous membrane above may herniate as small polypoid projections resembling a cockscomb. On palpation the margins of the stricture are found to be granular and, if the palpating finger can be introduced through the aperture, the mucous membrane above is found to be of normal consistency. It is my opinion that this is an abortive, nonprogressive type of the disease in the rectum which, after advancement to this stage, remains stationary; however, the mucous membrane just distal to the stricture is subject to trauma, ulceration and secondary infection, which, in most cases, leads to the formation of perirectal abscesses and fistulas. These annular diaphragm-like strictures are usually singular but may be multiple, occurring at different levels almost exclusively in the lower 6 cm. of the bowel.

The second type of stricture is usually from 2 to 6 cm. in length, funnel shaped and of india rubber consistency and feels granular on palpation. The smallest aperture of the funnel is at the proximal end of the stricture, where the infiltration stops abruptly. The mucous membrane above this site is normal, whereas that covering the lesion is characteristically hyperplastic and may have a glistening appearance. The mucous membrane below the stricture and the skin about the anus are commonly the seat of ulceration and polyposis.

Occasionally there is a third type of stricture, which may be very extensive, at times involving the entire bowel below the rectosigmoid junction. In one of our patients the process extended from the anus through the lower part of the bowel and into the distal opening of a barrel-shaped colostomy at the sigmoid flexure. Along the course of these lesions there may be levels at which the constriction is much more advanced than at others. It is possible that this type originates as isolated lesions at different levels in the bowel which gradually coalesce into one long tubular stricture.

Papillomas of the mucous membrane below the site of stricture are almost invariably present in all three types, and the skin about the anus is hyperplastic and often the site of condylomatous growths. The fistulas, if present, are usually multiple and open into the rectum just below the stricture. The stricture of the rectum may be found alone or associated with the other manifestations of the disease, constituting the genito-anorectal syndrome. In the advanced stages in women there may be more or less complete destruction of the rectovaginal septum, with the formation of rectovaginal fistulas. We have observed a patient in whom the destruction and infiltration by scar tissue of the perineum was so extensive that it was necessary that her child be born by cesarean section. These manifestations of venereal lymphogranuloma are not considered in this paper.

Although the clinical picture of the advanced stages has been described frequently, to our knowledge the early stages of the rectal lesion are seldom recognized as such. The patient in whom the disease occurs usually is not the type who seeks early medical advice. If he does, the early manifestations of venereal lymphogranuloma in the rectum are apt to go unrecognized or to be attributed to some other disease. In practically every series of cases reported in the literature, as in our own, a large percentage of the patients had been treated over a period of years without correct diagnosis. It is striking how many of these patients had been operated on for hemorrhoids, polyps, fissures or fistulas without improvement and with eventual formation of stricture. In many cases the formation of stricture had been falsely attributed to trauma resulting from operation. There is little doubt that a large percentage of the so-called postoperative traumatic strictures of the rectum would actually have formed without operation and that the operations performed were carried out without the surgeon's having recognized the true underlying pathologic process.

The early clinical manifestations are often indistinguishable from those of any other irritative lesion in the lowermost segment of the bowel. The earliest symptom is usually burning or pruritus of the skin about the anus, associated with more or less mucous discharge. The discharge may be so minimal that its presence is completely ignored by the patient. Examination at this time may reveal no more than

7. Finkelstein, B. K.: Operative Behandlung entzündlicher Verengerungen des Mastdarmes, Arch. f. klin. Chir. **168**: 547, 1932.

localized swelling of the mucous membrane of the anal canal or diffuse edema of the mucous membrane throughout the entire lower segment of the bowel. Digital examination may give entirely negative results. Examination with a short proctoscope often results in pouting of the mucous membrane into the orifice, which may well be falsely interpreted as an extrusion of internal hemorrhoids. The edema and swelling of the mucous membrane, whether localized or diffuse, usually persists for several weeks, after which time it gradually becomes hyperemic and bleeds easily when traumatized. Minute papillomatous outgrowths appear over the edematous part. Digital examination at this stage reveals the presence of single or multiple enlarged, indolent, somewhat movable glandular swellings lying immediately under the bowel wall. With a sigmoidoscope it is often possible to recognize these swellings, covered with intact mucous membrane, protruding into the lumen of the bowel. The edema of the mucous membrane, along with the swelling of the lymph glands, may disappear entirely, so that subsequent examination reveals a perfectly normal bowel. This is probably an abortive type of the disease which never advances past this stage and recedes spontaneously. In other cases the perirectal tissues in the vicinity of the glandular swellings gradually become infiltrated, so that on digital examination one finds localized areas of perirectal and then submucosal induration, which gradually spread until they have completely infiltrated the wall and encircled the lumen of the bowel.

The infiltration may take place in one localized segment, or it may appear concurrently at several different levels. These areas then spread longitudinally until they coalesce and become a single cylinder several centimeters in length enveloping the entire circumference of the bowel. We have never observed a patient long enough to see the advance of the disease in the rectum from its earliest manifestations to the late picture. However, we have seen localized edema of the mucous membranes, with underlying glandular swelling, advance to the stage of a limited cylindric fibrous stricture like a signet ring, with subsequent ulceration and formation of fistula. In our experience the discharge from the rectum remains mucoid until ulceration of the mucous membrane occurs, at which time it changes to a bloody mucopurulent discharge, seen in the late stages. It is difficult to explain the ulceration of the mucous membrane because, as a rule, it does not occur at the site of the stricture but rather in the mucous membrane immediately below. We have never actually observed ulceration of the mucous membrane resulting from suppuration of an underlying lymph gland, although, reasoning from the pathologic process which we know occurs in the inguinal lymph glands (in this particular manifestation of venereal lymphogranuloma), it would be reasonable to assume that the perirectal glands undergo the same changes and actually break down to form fistulas emptying into the rectum or into the perirectal tissues. One might seek proof of this contention in the fact that Frei antigen has been prepared successfully from pus obtained from sterile abscesses found in the region of the anus. The virus of venereal lymphogranuloma has also been demonstrated in the tissues about the rectum by intracerebral inoculation into monkeys. The persistent fistulas, however, are practically always secondarily infected and, in our experience, communicate almost invariably with the rectum or the anal canal at a site distal to the rectal stricture.

LYMPHATICS

In order to understand the role of venereal lymphogranuloma in the pathogenesis of rectal stricture it is necessary to review the circulation of lymph in the genital, anal and rectal regions in men and women. Briefly it may be summarized as follows: The superficial as well as the deep lymphatics of the glans penis and the prepuce drain primarily into the inguinal lymph nodes. These in turn drain into the iliac nodes. Many anastomoses exist between the lymphatics of the scrotum, the glans penis and the skin about the rectum. Occasional anastomoses exist between the lymph vessels of the anterior urethral mucous membrane and the scrotal and anal regions. The lymphatics of the scrotal skin empty primarily into the inguinal nodes but also join the main lymph channels leading from the testicles into the aortic nodes. An indirect anastomosis between the penis and the anorectal lymph nodes is established through the abundant lymphatic connections of the anal and the scrotal skin. The anorectal nodes have direct connections with the superior hemorrhoidal and sacral nodes through lymph channels situated in the posterior wall of the rectum. Although the drainage of the anterior part of the urethra is for the most part into the inguinal nodes, that of the posterior part is into the posterior lymphatic pedicles of the prostate gland, which empty into the rectal stalks and thence into the rectal absorbent pedicles.[8] This direct communication between the posterior part of the urethra and the perirectal glands is of great importance, as it is through these channels that infections of the posterior part of the urethra find a way into the lymphatics about the rectum.

In women the lymphatics of the urethra and the vulva drain principally into the inguinal nodes. Direct trunks lead from there to the iliac and the hypogastric nodes. The lymph vessels of the posterior portion of the vulva have direct connections with those about the anus, which, as in men, drain primarily into the inguinal nodes. There are, however, direct channels leading from the lymphatics about the anus into Gerota's nodes at the anorectal junction. There are also connections leading from the anal skin through lymph vessels in the posterior wall of the rectum into the sacral nodes. The lower third of the vagina has connections with the network of lymphatics about the anus as well as direct communications with the iliac and the hypogastric nodes. The middle as well as the upper portion of the vagina drains primarily into the iliac and the hypogastric nodes, although there are lymph vessels which penetrate the fascia of the rectum and anastomose with the lymphatics of the rectal wall. By this means there is established a direct communication between the vaginal wall and the anorectal glands of Gerota.[9]

It is generally believed that the sequelae of venereal lymphogranuloma, namely, elephantiasis of the genitalia, and anal and rectal strictures, do not occur as frequently in men as in women, the explanation being that the lymph vessels in men lead from the primary lesion on the glans penis or prepuce to the inguinal glands. In women the disease is not usually manifested by inguinal adenitis, for the lymphatics drain from the primary lesion mostly to the deep pelvic glands, causing lymph stasis in the genital, anal and rectal regions. Our experience has shown that rectal involvement in men

8. Nesselrod, J. P.: Proc. Staff Meet., Mayo Clin. **11**: 369 (June 10) 1936.
9. Barthels, C., and Biberstein, H.: Beitr. z. klin. Chir. **152**: 161 (April), 325, 464 (May) 1931.

is not at all infrequent and is dependent on the site of the primary lesion. Infections of the posterior part of the urethra with the virus, as well as primary lesions in or about the anus, in the male are usually followed by rectal involvement. On the other hand, primary lesions on the clitoris and the vulva in the female lead to inguinal involvement alone. In our experience the site of the primary lesion determines the nature of lymphatic involvement and the type of secondary lesion regardless of sex.

While the majority of investigators have come to the conclusion that the etiologic factor in the production of benign strictures is to be found in disturbances of lymph flow, the exact nature of this disturbance is not known. Chronic lymph stasis is thought by some to lead to disturbances in nutrition in the parts affected, which in turn may lead to ulceration, proliferation of connective tissue, elephantiasis and, finally, shrinkage and stricture.

The lymphatic channels about the rectum are subject to a great deal of variation, which in all probability accounts, in part at least, for the various types of lesions produced by their infiltration. Feilchenfeld [10] has suggested that in cases in which rectal stricture is unassociated with other features of the syndrome the initial lesion probably occurred about the anus. We are of the same opinion. In our experience it is rare to find rectal lesions in men associated with any of the other late manifestations of the disease. In a large percentage of our male patients we have been able to obtain a history of abnormal sexual practices. It is also rare to see a man in whom inguinal adenopathy has preceded rectal involvement. Inguinal adenopathy associated with rectal stricture is usually the result of secondary infection. We have one patient whose primary lesion was unquestionably on the penis, resulting in typical inguinal adenopathy and in subsequent rectal involvement. This patient, however, had so-called nonspecific urethritis immediately after the initial lesion on the penis. The rectal involvement was probably the result of posterior urethritis with extension through the lymphatics of the posterior part of the urethra and the prostate into those about the rectum. The rectal involvement in this patient is extensive. This is probably a more common mode of rectal involvement in men than is generally recognized. In many of our male patients the rectal involvement followed urethritis of unknown cause. Urethritis due to the virus of venereal lymphogranuloma has been reported frequently and may possibly accompany gonorrheal infections of the urethra.

We have one patient under treatment at present who, after nonspecific urethritis, had a periurethral abscess, perineal fistulas and, subsequently, a rectal stricture and rectal fistulas. This sequence of events supports our contention that infection of the posterior part of the urethra with the virus may well result in perirectal lymphatic involvement and eventually in rectal stricture. Löhe and Rosenfeld [11] said that there may possibly be not only an obstruction to the lymph flow but an accompanying retrograde flow of infectious material from the pelvic glands into the skin of the infected region and into the rectal wall, so that the resultant changes are, at least in part, specific ones due to the virus of venereal lymphogranuloma. Dick made the interesting observation that the inflammatory processes seen in association with venereal lymphogranuloma do not subside after colostomy, as do the common infections seen after carcinoma of or injury to the bowel. This might be interpreted as some proof of the specific nature of the infection.

10. Feilchenfeld, H.: Elephantiasis of Vulva, Anus and Rectum, Med. Klin. **28**: 965 (July 8) 1932.

11. Löhe, H., and Rosenfeld, H.: Neue Ergebnisse über die Späteformen des Lymphogranuloma inguinale, Med. Klin. **28**: 1486 (Oct. 21) 1932.

PATHOLOGY

It is important to remember that in the pathologic picture associated with rectal stricture the entire process takes place at a site where any sort of damage to the tissues will result in nonspecific infection. It would seem from our own experience that secondary infection of the tissues of the rectum plays an important part in the formation of stricture. It seems apparent that the early changes in the rectal wall are due to lymph stasis following infiltration of the regional lymphatics with the virus of venereal lymphogranuloma. The virus has been isolated from the perirectal tissues about these strictures; however, there is not sufficient proof at present that the strictures are entirely of this origin.

The histologic picture of the tissues involved in inflammatory stricture of the rectum has been described in cases in which the whole rectum was removed at operation. Although Barthels and Biberstein [12] expressed the opinion that the histologic changes in the rectum are pathognomonic of the disease, we have not been able to recognize them as such. These authors, as quoted by Stannus,[6] described the pathologic picture in one of their cases as follows:

> In case 2 the ampulla showed radiating scars, ulceration and some thickening of the wall; the mucous membrane of the rectum was slightly edematous and injected as far as the sigmoid. The lining epithelium in the lower part was flattened and metaplastic (leukoplakia) with cellular edema. Beneath this there was a diffuse small-celled infiltration composed of lymphocytes, plasma cells, eosinophils, polynuclears and some epithelioid cells and newly formed capillaries. Deeper still was noted an irregularly disposed connective tissue made up of bands of fibers showing edema and hyaline change and the structureless remains of muscle fibers. The normal structure of the bowel wall had been lost. In the middle layers of the wall of the ampulla characteristic minute star-shaped abscesses were found. These for the most part did not open towards the lumen of the bowel, but ran obliquely through the tissues. Their walls were composed of epithelioid cells and their contents consisted of lymphocytes, plasma cells, eosinophils with some polynuclears. Elsewhere small foci of infiltration up to the size of a millet seed were noted, composed of the same cell elements with tiny central areas of necrosis, forming what have been called miliary gummata. In some sections giant cells were numerous, in others none were discovered. Close to the necrotic foci, stained cell nuclear remains were in evidence. The normal tissue was entirely replaced by an abnormal granulation tissue. Some of the infiltrations were made up almost entirely of epithelioid cells or young connective tissue cells. These tiny granulomata had an appearance that suggested they were formed in minute lymph nodes. In the lymph glands of the adjacent perirectal fatty tissue in which the lymph sinuses were dilated similar cell elements were seen, forming little lymph thrombi lying in situ. Perivascular or, as has been pointed out elsewhere, what is more correctly described as paravascular infiltration was marked. It is an infiltration of the lymph spaces running in the sheaths of the vessels. In the perirectal fatty envelope close to the external wall of the rectum an obliterating arteritis was manifested; the media was unrecognizably fused with the other coats of the vessel. The veins showed changes in their walls resulting from an infiltration from without. In a section of the wall of the rectum at 7 cm. above the anus the changes were much the same. In sections taken at 20 cm. above the anus the changes were most marked in the mucous membrane and less in the walls of

12. Barthels, C., and Biberstein, H.: Zur Histogenese der nach Lymphogranulomatosis inguinalis auftretenden Rektumstrikturen, Beitr. z. klin. Chir. **152**: 464 (May) 1931.

the bowel. There was a marked proctitis with partial destruction of the epithelial lining, but the subjacent layers preserved their structure and did not show the same results of chronic inflammation, though in the middle layers of the wall of the rectum small areas of infiltration were present similar to those seen in sections of the lower part of the wall of the rectum. In the ampulla, therefore, the changes in the mucous membrane are of minor degree, while there is marked infiltration and replacement of normal tissue in the submucous layers and perirectal connective tissue. Above the ampulla the changes are more marked in the mucous membrane and comparatively slight in the rest of the bowel wall.

In our opinion this pathologic picture may well represent nonspecific inflammatory changes which have taken place in tissues the resistance of which has been greatly lowered by the destruction of their lymphatic drainage. Although specific changes may take place after invasion of the tissues with the virus of venereal lymphogranuloma, we have been unable to recognize them histologically as such except in the lymphatics. As the late changes in the rectum are invariably associated with secondary infection clinically, it seems reasonable to assume that the histologic picture in the rectum may also be explained on this basis.

PATIENTS STUDIED

Eighty-nine patients have been treated for benign rectal stricture in the San Francisco Hospital since July 1, 1919. The histories of seventy-eight were complete enough so that a definite conclusion might be drawn as to the nature and localization of the disease. The remaining histories contained insufficient data and were discarded. Of the seventy-eight patients sixty were men and eighteen women. Twelve patients were Negroes, and nine of the remaining sixty-six white persons were Mexicans. Forty of these patients entered the hospital before the introduction of the Frei test; a diagnosis of syphilitic stricture was made in twenty-one cases (in nine apparently on the sole basis of a past history of syphilis), of gonorrheal proctitis in twelve, of tuberculosis in three and of traumatic stricture in four (in three of stricture following childbirth and in one of stricture following hemorrhoidectomy). A critical analysis of these histories in view of our present knowledge of the role of venereal lymphogranuloma in the pathogenesis of benign rectal stricture would bring all but four of these cases into the category of this disease.

The remaining thirty-eight patients were seen and studied by me, and in all of them a positive intradermal reaction to the virus of venereal lymphogranuloma was obtained. In eleven patients a localized annular stricture was found, in eighteen the characteristic funnel-shaped stricture and in five a far advanced tubular stricture involving the greater part of the bowel distal to the rectosigmoid junction. Four patients were seen in the early stages of the disease and presented the picture of acute proctitis with perirectal glandular enlargement.

We were able to obtain a definite history of abnormal sexual practices from over half of the patients studied. It is interesting to note that only two of the men studied had ever been married, although the ages of the patients ranged from 19 to 72 years. Negative clinical and serologic evidence of syphilis was obtained in enough cases to rule out this disease as an etiologic factor.

TREATMENT

The treatment of inflammatory stricture of the rectum is in general unsatisfactory. Many different types of treatment suggested in the past have, after due trial, been discarded. The use of many of the drugs suggested in the literature for both local and systemic treatment has been followed by discouraging results in our hands. Roentgen rays and radium are of little or no value. The destructive nature of the disease is such that it leads to irreparable damage of the tissues so that, in the advanced stages, one can hope only to prevent extension, to relieve symptoms as they develop and to combat the ravages of secondary infection. In the early stages it is possible that the intracutaneous and intravenous use of Frei antigen in an attempt to desensitize the patient to the virus may be useful. We believe that in certain of our patients desensitization therapy has enabled us to prevent or at least check the advancement of the disease to the destructive lesions seen in the late stages. If the disease in the rectum is recognized early, intensive desensitization over a long period is justified. At the same time it is necessary to realize that superimposed secondary infection must be prevented at all costs. Unnecessary surgical procedures about the rectum in the presence of lymph stasis due to the virus of venereal lymphogranuloma necessarily lead to the opening of channels to secondary infection which otherwise might be prevented. In all patients the lower part of the bowel should be kept as clean as possible. Avoidable constipation should be prevented, and measures should be instituted to keep the skin about the anus as clean as possible. When perirectal abscesses form they should be drained by wide incision, and every attempt should be made to find their communication with the lumen of the bowel, so that when fistulous tracts develop they may be excised in toto and their communication with the bowel widely incised. Radical surgical procedures in the presence of rectal stricture are not to be feared, for one can hope for nothing more than the eradication of the disease in the tissues by the formation of fibrous tissue.

It is well known that the inflammatory processes seen in association with venereal lymphogranuloma do not subside after colostomy, as do infections which follow carcinoma or injuries to the bowel. In our opinion one is rarely justified in performing a colostomy. The patient continues to have his rectal symptoms, as before, and in addition must live with an artificial anus. Although we have seen two patients in whom the inflammatory rectal stricture led to complete obstruction of the bowel, the condition was relieved by local dilation, and recurrent obstruction was prevented by regulation of the diet and the administration of liquid petrolatum. Many patients received considerable relief by treating their lower bowel as they would an artificial anus, that is, by the use of an early morning enema and regulation of their bowel habits by diet. Patients with thin annular strictures may often be relieved of their obstructive symptoms by simple local excision of a portion of the stricture. Radical surgical excision of the rectum, as suggested in Germany by Schede,[5] seems to us unjustifiable. We have seen two patients so treated in whom the disease continued to advance after excision and secondary infection led to extensive abscess and fistula formation.

In our opinion repeated dilation of the strictures by mechanical means leads to unnecessary trauma and should be utilized only in cases in which complete obstruction is imminent. At present we would suggest that in every case an attempt be made to prevent the spread of infiltration with the virus by the use of intracutaneous and intravenous injections of Frei antigen,

that each patient be instructed how he may keep himself clean by the use of sitz baths, enemas and proper diet, and that secondary infection be controlled by intelligent surgical intervention.

SUMMARY AND CONCLUSIONS

Eighty-nine patients with benign rectal stricture were seen at the San Francisco Hospital from 1919 to 1937. Seventy-eight patients were studied; in seventy-four the condition was considered to be the result of infection with the virus of venereal lymphogranuloma.

The disease occurred in sixty men and fourteen women; twelve were Negroes and nine were Mexicans.

Thirty-eight patients were tested with the intradermal injection of Frei antigen, and in every case a positive reaction was noted.

Early recognition of the disease is important.

Rectal involvement in men occurs mainly after infection with the virus of the posterior part of the urethra or as a result of primary lesions in the region of the rectum.

The intradermal and the intravenous use of Frei antigen is helpful when associated with proper surgical care of the secondary infection involved. The use of dilators and radical removal of the rectum are not advisable.

MENTAL SYMPTOMS ASSOCIATED WITH BRAIN TUMOR

A STUDY OF 530 VERIFIED CASES

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Our purpose in this investigation was to ascertain the frequency of occurrence, the nature and the localizing value of mental symptoms in cases of tumor of the brain. In previous communications we described the mental symptoms in patients with tumor of the frontal lobe [1] and temporal lobe [2] and compared them with the mental symptoms of patients with tumor located below the tentorium.[3] In the present paper we are reporting in brief the psychic disturbances in patients with a tumor located in any part of the brain. The study was based on personal observations of 530 patients with expanding intracranial lesions in whom the diagnosis was confirmed by operation, necropsy or both. The location of the tumors and their histologic nature are recorded in table 1.

Abnormal mental reactions play an important rôle in the symptomatology of tumor of the brain. The reactions may occur at any time during the course of the disease. In many cases they are the earliest and in some the first symptoms of the ailment, preceding by weeks, months or even years the neurologic evidences of intracranial expanding lesion. Some patients with tumor of the brain have a genuine psychosis, for which they are admitted to a hospital for mental diseases. In such institutions the presence of a tumor may not be recognized until necropsy. On the other hand, in patients with a definite psychosis of endogenous or exogenous etiology, a tumor of the brain may develop in the course of the psychosis as an independent condition. Although one would expect the mental picture of a tumor of the brain to assume the characteristics of the so-called organic reaction type, clinical experience shows that this is not always the case.

Unusual difficulties may be encountered in the evaluation of mental symptoms in a case of brain tumor in persons suffering from cerebral arteriosclerosis prior to the appearance of symptoms and signs of a focal lesion in the brain. In such cases one must be guided solely by the history of the patient's previous mental condition. Ordinarily it is impossible to make an exhaustive and satisfactory investigation of the patient's personality before the appearance of symptoms of brain tumor, especially with the patient in the state in which he usually is when he is hospitalized.

Another disturbing factor in the evaluation of mental symptoms in cases of brain tumor is the frequent occurrence of the convulsive state. In many patients the abnormal state due to the presence of an intracranial growth may be wrongly interpreted and attributed to idiopathic epilepsy.

The actual determination of the absence or presence of mental symptoms may be difficult in some cases of brain tumor owing to disturbances in the patient's speech. The presence of motor or sensory aphasia, apraxia or even dysarthria may so interfere with the patient's ability to communicate his thoughts to the examiner that the results obtained from the psychiatric examination are rendered difficult to interpret. The mental capacity and the emotional state of most of these patients could be determined only by observing their reactions in the wards and by their mode of adjustment to the hospital routine.

Our material was analyzed from the point of view of disturbances in the sensorium, affect (including euphoria and facetiousness), memory and orientation, intellect and higher psychic functions, hallucinations, and sphincteric disturbances. Transitory abnormal mental reactions associated with convulsive seizures, epileptic equivalents (except uncinate phenomena) and those following intracranial injections of air or operations were not regarded by us as mental symptoms of tumor and were therefore not included in this study.

Unusual difficulties were encountered in the attempt to determine the presence or absence of changes in personality. Strictly speaking, a patient who shows symptoms of any disease, physical or mental, exhibits a change in his psychosomatic integration, and consequently a change in personality. To draw conclusions from descriptions given by friends or relatives as to the patient's change in personality would be pure conjecture. Therefore the heading "changes in personality," used in our previous classifications of mental symptoms in brain tumor, was omitted here.

Our method of approach in analyzing the various mental symptoms seemed to be the most feasible for our purposes. By employing this method we do not wish to imply that there exists a definite separation of the various psychic functions; for example, of intellect and emotion, or of memory, intellect and emotion. We do not mean to revert to the old psychologic theory which conceived of mind as an aggregate of compartments into each of which, as White [4] said, "was pigeonholed a special faculty such as feeling,

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1. Strauss, Israel, and Keschner, Moses: Mental Symptoms in Cases of Tumor of the Frontal Lobe, Arch. Neurol. & Psychiat. **33**: 986 (May) 1935.

2. Keschner, Moses; Bender, Morris B., and Strauss, Israel: Mental Symptoms in Cases of Tumor of the Temporal Lobe, Arch. Neurol. & Psychiat. **35**: 572 (March) 1936.

3. Keschner, Moses; Bender, Morris B., and Strauss, Israel: Mental Symptoms in Cases of Subtentorial Tumor, Arch. Neurol. & Psychiat. **37**: 1-18 (Jan.) 1936.

4. White, W. A.: Outlines of Psychiatry, ed. 3, Washington, D. C., Nervous & Mental Disease Publishing Company, 1911, p. 6.

thinking, and volition, each one of which was considered distinct from the others." We fully realize that an abnormal mental state is the expression of an interference with the functioning of the various mechanisms subserving the sensorium, association, perfection and elaboration of sensory impressions, affect, memory and orientation, speech and intellect, and the sum total of these, behavior.

A survey of the literature on the symptomatology of tumor of the brain discloses that some observers have reported the presence of mental symptoms in only 8 per cent of cases while others have found them in every case.[5] This statistical disparity is encountered in the reports not only as to frequency but also as to the nature of the mental symptoms. This may be due to the superficiality and haste with which most patients with tumor of the brain are studied psychiatrically. Routine, painstaking examinations of the mental reactions of these patients may reveal abnormalities which are so fine that they escape detection.

TABLE 1.—*Location and Histologic Nature of Tumors*

Type of Tumor (Histology) and Location in Brain	Number of Cases in Each Group	All Types of Gliomas	Meningiomas	Metastatic Carcinomas	All Types of Sarcomas	Neurofibromas	Pituitary Adenomas	Tumors of Hypophysial Stalk	Pinealomas	Tuberculomas	Papillomas	Angiomas	Cholesteatomas	Osteochondromas	Gumma	Colloid Cyst	Cysticercus Cyst	Unclassified Cyst	Unclassified Tumor	Ependymomas	Glioma and Carcinoma in Same Patient
Multiple	29	4	1	17	5	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	1
One hemisphere	13	12	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..
Bifrontal	15	8	6	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Frontal	53	28	17	5	2	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..
Frontoparietal	27	15	10	1	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..
Frontoparietotemporal	15	8	6	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..
Frontotemporal	21	8	8	..	..	1	..	..	..	1	1	..	1	1	..	..	..	..	..	..	..
Temporal	56	38	11	2	3	1	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..
Temporo-occipital	12	6	..	3	1	..	..	..	..	..	2	..	..	..	..	..	..	..	..	..	..
Temporoparietal	18	11	1	1	2	..	..	..	..	..	..	..	..	..	..	..	..	1	2	..	..
Temporoparieto-occipital	13	11	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Parietal	32	16	8	4	..	..	..	..	..	..	..	2	..	..	1	..	..	1	..	..	..
Parieto-occipital	11	7	1	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..
Occipital	11	4	2	2	1	..	..	..	..	..	1	1	..	..	..	..	..	..	..	..	..
Basal ganglions and lateral ventricle	14	14	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Intrasellar and suprasellar	36	..	4	..	..	..	16	15	..	..	..	..	..	..	..	..	..	..	1	..	..
Third ventricle	15	7	..	..	1	4	..	..	..	..	..	..	..	..	..	1	..	..	1	1	..
Pineal	10	1	..	..	..	..	..	..	9	..	..	..	..	..	..	..	..	..	..	..	..
Cerebellar	74	42	11	7	6	..	..	..	..	3	..	..	..	..	..	..	..	..	5	..	..
Cerebellopontile angle	36	1	5	..	2	27	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..
Brain stem	19	11	6	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	1	..	..
Total supratentorial	401	198	77	37	16	6	16	15	9	2	4	3	3	2	1	1	0	3	6	1	1
Total infratentorial	129	54	22	7	8	27	..	..	..	3	..	..	..	..	..	..	1	..	7	..	..
Grand total	530	252	99	44	24	33	16	15	9	5	4	3	3	2	1	1	1	3	13	1	1
Without mental symptoms	118	48	21	3	4	21	2	2	2	4	..	2	1	..	1	..	..	..	7	..	..
Percentage of each type of tumor without mental symptoms	22	19	21	7	16	64	13	13	22	80	..	66	33	..	100	..	..	..	54	..	..

DISTURBANCES OF THE SENSORIUM, INCLUDING HALLUCINATIONS

Under disturbances in the sensorium we included the various degrees of increased threshold of consciousness. These were described most commonly as drowsiness, torpidity, somnolence and semistupor. In some cases the descriptive terms "apathy" and "dulness" were used in conjunction with the foregoing terms. Fluctuation in the limen of consciousness was the outstanding characteristic. Lucid intervals, varying from hours to days and even weeks, were not infrequent. Disturbances in sensorium were present in 363 patients (61 per cent) and had practically no localizing value.

Hallucinations were observed most frequently in patients with supratentorial tumor. They were recorded in 103 instances.[6] (19 per cent.) The types of hallucinations, in the order of their frequency, were crude auditory, crude visual, formed visual, olfactory, formed auditory, gustatory and haptic. The hallucinations were usually fleeting in character. In many instances the patients had no insight, but from their behavior it was evident that they reacted to hallucinations.

The crude auditory hallucinations, noted in patients with tumor above the tentorium and in whom the peripheral neural pathways were not diseased, were described as ringing, hissing, whistling, gushing water, buzzing or grinding. These sounds were heard most often in the ear on the side of the tumor. Complex auditory hallucinations occurred only in patients with supratentorial tumor; these patients heard melodies or speaking voices.

Patients with crude visual hallucinations complained of seeing flashes of light, colored spots, rings or colored lights. Crude visual hallucinations were observed in patients with tumors located above and, to a lesser extent, in patients with tumors located below the tentorium.

Complex visual hallucinations were unusual in cases of infratentorial tumor.[3] The patients who had complex visual hallucinations saw people or objects that frequently appeared in one field of vision. Usually the object seen in the hallucination was in motion and had a bizarre appearance. Variations in the size of the hallucinatory objects visualized, such as micropsia (lilliputianism) and macropsia (gigantism), were noted in one case. Déja vu phenomena, sometimes attributed to lesions of the temporal lobe, were conspicuously absent in this series of patients.

5. Schuster, P.: Psychische Storungen bei Hirntumoren, Stuttgart, 1902. Knapp, P. C.: The Mental Symptoms of Cerebral Tumor, Brain **29**: 35, 1907. Baruk, H.: Les troubles mentaux dans les tumeurs cerebrales, Paris thesis, 1926. Henry G. W.: Mental Phenomena Observed in Cases of Brain Tumor, Am. J. Psychiat. **12**: 414 (Nov.) 1932.

6. This number does not include the instances of paresthesias or other haptic hallucinations in patients with tumor involving the parietal lobe or of tinnitus in patients in whom the tumor was located below the tentorium.

Most patients with olfactory hallucinations complained that they smelled disagreeable odors. Olfactory hallucinations were recorded in patients in whom the tumor was located usually on the undersurface of the cerebral hemispheres.

Three patients had gustatory hallucinations; two complained of a bad taste, and one of a sweetish taste.

Localized paresthesias or the abnormal sensations described as jacksonian sensory fits were most commonly found in patients with tumor of the parietal lobe opposite to the side of the haptic hallucinations. Several patients stated that they felt bugs creeping over the head and body. Some patients had hallucinations in two or more spheres. Dream states and uncinate fits were not infrequently associated with olfactory or with gustatory hallucinations.

and a few had spells of involuntary crying and laughing. Suicidal trends were rare. When the patient realized that he was seriously ill, he reacted in some form of depression. A few patients, however, were depressed before they became aware that they were ill.

In our series it was found that irritability or some form of mental depression frequently appeared early in the course of the disease. It was not until insight and judgment had become defective, and this occurred in most instances late in the course of the disease, that other disturbances in the affect, such as euphoria and facetiousness, made their appearance. Although facetiousness was slightly more common in patients with tumor of the frontal lobe, the general incidence of this symptom was so low that not much localizing significance could be attached to it. Euphoria and facetious-

TABLE 2.—*The Incidence and Type of Mental Symptoms and Location of the Tumor in Brain*

Type and Location of Tumor	Number of Cases in Each Group	One or More Mental Symptoms in Same Patient	Changes in Sensorium	Changes in Affect	Euphoria and Facetiousness in Same Patient	Euphoria	Facetiousness	Euphoria or Facetiousness or Both	Memory or Orientation or Both	Changes in Intellect and Higher Psychic Functions	Sphincteric Disturbances	Mental Changes as Early Symptoms of Brain Tumor	All Types of Mental Changes in Same Patient	All Types of Hallucinations	Delusions
Multiple	29	29	23	23	4	4	1	9	18	18	10	7	13	10	4
One hemisphere	13	10	8	5	0	3	0	3	3	3	2	0	0	2	0
Bifrontal	15	13	12	10	6	0	2	8	9	10	5	5	8	1	1
Frontal	53	45	32	30	6	3	7	16	25	22	13	12	10	9	4
Frontoparietal	27	22	15	13	3	3	1	7	9	8	2	4	3	6	1
Frontoparietotemporal	15	13	11	8	1	2	0	3	10	5	6	3	1	3	2
Frontotemporal	21	17	15	11	3	2	1	6	10	11	3	4	7	4	4
Temporal	56	52	42	34	6	7	4	17	32	28	11	16	17	18	3
Temporo-occipital	12	12	11	4	0	1	0	1	4	6	1	0	1	3	1
Temporoparietal	18	17	14	7	2	0	1	3	6	5	2	3	1	4	1
Temporoparieto-occipital	13	11	9	6	1	2	0	3	7	5	0	2	0	4	0
Parietal	32	26	22	12	0	0	0	0	8	12	2	6	3	7	1
Parieto-occipital	11	9	8	7	2	0	0	3	7	7	4	4	6	4	0
Occipital	11	9	7	5	1	1	0	2	5	4	3	1	3	3	0
Basal ganglions and lateral ventricle	14	13	10	10	1	1	0	2	7	7	3	2	5	2	2
Intrasellar and suprasellar	36	32	22	20	5	3	2	10	12	15	6	2	7	9	3
Third ventricle	15	13	8	6	2	0	0	2	7	7	4	1	4	3	0
Pineal	10	8	6	4	0	3	0	3	2	5	0	1	0	3	0
Cerebellar	74	35	30	16	2	4	1	7	5	7	7	4	3	5	1
Cerebellopontile angle	36	15	9	9	1	1	1	3	4	5	1	1	1	2	0
Brain stem	19	11	9	5	0	1	0	1	1	4	1	2	0	1	0
Total supratentorial	401	351	275	215	43	36	19	98	181	178	77	73	80	95	27
Total infratentorial	129	61	48	30	3	6	2	11	10	16	9	7	4	8	1
Grand total	530	412	323	245	46	42	21	109	191	194	86	80	93	103	28

From these observations it is evident that the occurrence of hallucinations other than tinnitus in a patient with tumor of the brain makes it probable that the tumor is located above rather than below the tentorium. Further localization of the tumor in the brain may be ventured from the following observations: The presence of complex visual and auditory hallucinations suggests that the tumor might be growing in the temporal lobe; complex visual hallucinations in one lateral field of vision would place the tumor in the temporal or occipital lobe opposite to the side of the field of visual hallucinations.[2] Localized haptic hallucinations are most commonly found in patients with tumor of the parietal lobe on the side opposite to the hallucination. Tinnitus, whether present in patients with supratentorial or infratentorial tumor, is usually on the side of the tumor.

CHANGES IN AFFECT

The general mood of patients with brain tumor was that usually observed in organic diseases of the brain. Disturbances in the affect were present in 245 patients (46 per cent). Hyperirritability, depressions and states of anxiety were frequent symptoms. Emotional instability was also common; many patients cried readily, ness were not specific for any one location of the brain. The latter observation is in agreement with the conclusions of a majority of authors, especially as it relates to mental symptoms in patients with frontal lobe tumor. Emotional disturbances in patients with brain tumor are of no localizing value; such disturbances may occur in individuals with tumor situated in any part of the brain.

CHANGES IN INTELLECT AND THE HIGHER PSYCHIC FUNCTIONS

Defects in memory and in orientation varied in severity in the same and in different patients. The most common disturbance was in the recent memory. Several patients confabulated freely. In many instances confusional states were noted, and these were usually transitory. Disorientation, associated with defects in memory, was observed in patients with severe mental impairment. Disturbances in memory and in orientation were predominantly more frequent in patients with tumor above the tentorium; in 181 patients (45 per cent) with tumor above the tentorium and in only ten patients (9 per cent) with tumor below the tentorium. From this standpoint, these symptoms may have localizing value. The value, however, is slight.

CHANGES IN INTELLECT AND HIGHER PSYCHIC FUNCTIONS

Under disturbances in the intellect and higher psychic functions we included psychomotor retardation, poor reasoning ability, poor autocriticism, mental fatigability, poor calculation, mental deterioration, chronic confusional states and deliriums. Again these disturbances were more common among patients with supratentorial tumor rather than in those with infratentorial tumor. Changes in intellect and higher psychic functions were found in 178 patients with supratentorial tumor (44 per cent) and in sixteen patients with infratentorial tumor (12 per cent).

SPHINCTERIC DISTURBANCES

The sphincteric disturbances were most often in the form of urinary retention or incontinence. When the mental symptoms were severe and manifold, there also occurred incontinence of feces. Sphincteric disturbances have little localizing significance. They were recorded in eighty-six instances (16 per cent) of the entire series.

MENTAL CHANGES IN ALL PSYCHIC SPHERES

A patient was regarded as having changes in all psychic spheres whenever he presented the clinical picture of a psychosis such as that found in any type of organic disease of the brain. Some of these patients presented mental symptoms similar to those exhibited by patients with dementia paralytica, Alzheimer's disease or Korsakoff's psychosis. In a small number of patients the mental picture simulated the affective psychoses, such as manic depressive insanity or schizophrenia. There was no psychosis or mental syndrome that was found to be characteristic of brain tumor.

Disturbances in all psychic spheres among patients with tumor above the tentorium occurred in eighty-nine cases (22 per cent), while among patients with tumor below the tentorium there were four cases (3 per cent).

MENTAL CHANGES AS EARLY SYMPTOMS OF BRAIN TUMOR

In most patients with tumor of the brain, mental disturbances occur, as a rule, late in the course of the ailment. Mental changes as early symptoms occurred more frequently in patients with supratentorial tumor (seventy-three cases, or 18 per cent) than in patients with infratentorial tumor (seven cases, or 5 per cent). When mental symptoms appear early in the disease they are usually mild and may be varied in type. In our series the mental symptoms that appeared early were, in order of their frequency of occurrence, defects in memory, irritability, drowsiness, emotional instability, anxiety, depressed states, intellectual enfeeblement, paranoid trends, complex and crude hallucinations, euphoria, facetiousness and sphincteric disturbances. As early symptoms, mental changes were slightly more common in patients in whom the duration of symptoms before the recognition of the tumor was short. As a corollary to this it was found that, in patients with slow growing tumors in whom the symptoms were mild and of long standing before the tumor was recognized, mental disturbances as early symptoms were uncommon. For instance, of thirty-six patients with hypophysial tumor, in whom the course of the disease was of long duration, only two had mental changes as early symptoms. The foregoing observations appeared more striking when mental changes were considered from the standpoint of initial symptoms of brain tumor.[7]

A term often used to describe mental symptoms that occurred early in the course of brain tumor was "changes in character." Relatives complain that the patient seems to have changed in his manner or behavior; if the patient was of a jolly and congenial disposition before the illness he became morose and irritable; if he was energetic and enterprising, he became lazy and indifferent. Some patients who later became placid were described as "neurotic" and irritable in their premorbid state.

Psychogenic reactions were frequently observed in patients who had insight into their condition. The type and degree of reaction were expressions of their premorbid personality. These patients were concerned about their illness and the consequences that might ensue. Some exaggerated their symptoms. By themselves these mental reactions were not considered as mental symptoms of brain tumor in the sense in which we employed them in this investigation.

MENTAL SYMPTOMS IN RELATION TO THE LOCATION OF TUMOR IN THE BRAIN

The most varied and severe psychic disturbances were found in patients with multiple tumors of the brain. Almost as equally pronounced were the mental symptoms in cases of tumor of both frontal lobes. There was no mental syndrome that was strictly characteristic of any one area of the brain. The similarity in incidence and nature of mental symptoms of the frontal and temporal lobes have been discussed previously.[2] The only appreciable differences noted between the two were the type and the incidence of hallucinations. Olfactory and complex visual and auditory hallucinations predominated in the cases of tumor of the temporal lobe. Facetiousness was somewhat more frequent in patients with tumor of the frontal lobe, and hypokinesia, though present in both frontal and temporal was also somewhat more frequent in the cases of frontal lobe tumor.

Patients with tumor of the parietal lobe showed fewer mental symptoms than those in whom the tumor was in the frontal, temporal or even occipital lobe. The presence of haptic hallucinations on the side opposite to the tumor was of localizing value; it usually implied involvement of the parietal lobe.

Except for qualitative changes in the affect in patients with aphasia, there was no significant difference in the mental symptoms caused by tumors of the left and those caused by tumors of the right side of the brain. When a patient with aphasia realized that his speech was faulty, usually because of anomia, he became worried and depressed. When he did not realize that his speech was faulty, he failed to understand why his words brought no adequate response from people with whom he was conversing or why they attempted to communicate with him by what was to him a meaningless succession of sounds, owing to auditory aphasia. Consequently he became annoyed, irritable and sometimes very excited. Not infrequently he gave up in despair and became depressed.

There was no noteworthy difference in the mental symptoms in patients in whom the tumor was located in and about the ventricular system, as compared with those in whom the tumor was located in other parts of the cranial cavity. In cases of hypophysial tumor, mental symptoms were seldom early manifestations of the disease.

The mental symptoms in patients with tumor below the tentorium found in sixty-one cases (47 per cent) were much milder and less complex than those in the

7. Strauss, Israel: The Initial Symptoms and Early Diagnosis of Tumor of the Brain, Bull. New York Acad. Med. **12**: 467 (Aug.) 1936.

patients with tumor above the tentorium found in 351 cases (87 per cent). Marked mental changes occurred, sometimes in patients with infratentorial tumor, but not nearly as frequently as in patients with supratentorial tumor. Except for tinnitus on the side of the tumor, hallucinations in patients with posterior fossa tumor were rare and, when present, were of the crude visual type.

This study would seem to show that mental symptoms by themselves have little or no value in localizing a tumor of the brain. All that can be said is that (1) mental symptoms are more frequent, severe and varied and more apt to appear early in the disease in patients with supratentorial tumor; (2) complex visual and auditory hallucinations are more frequent in tumors of the temporal lobe than in those of any other portion of the brain.

PATHOGENESIS OF MENTAL SYMPTOMS IN CASES OF BRAIN TUMOR

It is impossible to state with any degree of certainty which factors were responsible for the mental reactions (organic type) in patients with tumor of the brain. We found that the most pronounced mental disturbances were observed in patients in whom the tumor involved both cerebral hemispheres. A large amount of tissue destroyed in the cerebral hemisphere on one side (hemispherical tumors) did not cause the severe and psychic changes that resulted when even a smaller amount of tissue was destroyed in cerebral hemispheres on both sides. The bifrontal, corpus callosum and multiple tumors gave the most varied, most pronounced mental symptoms in almost every instance. The more rapidly the symptoms of a brain tumor appeared, the greater was the possibility that mental symptoms would be manifest. The rapidity of the growth of the tumor was a determining factor in the frequency of occurrence and severity of the mental symptoms. Among the patients in this series who did not show mental symptoms, the tumors were predominantly of the slow growing type; e. g., pituitary adenoma, astrocytoma, neurofibroma, meningioma, tuberculoma, angioma and gumma. It was difficult to ascribe mental symptoms to intracranial hypertension because intracranial hypertension was present in a majority of patients with tumor of the brain. This was particularly evident in individuals with tumor of the posterior fossa. Despite this, mental changes—even changes in the sensorium, which some authors ascribe to increased intracranial pressure [5]—were not nearly as common in patients with tumor below the tentorium as they were in those with supratentorial tumor. Intracranial pressure may, however, be a contributing factor when it increases suddenly or rapidly. The age, general condition and premorbid personality of the patient were factors that modified the nature of psychic reaction to physical symptoms produced by the tumor.

SUMMARY AND CONCLUSIONS

1. A series of 530 patients with brain tumor was studied in order to determine the frequency of occurrence, nature and localizing value of abnormal mental reactions during the course of the disease.

2. There are no mental symptoms that are specific for brain tumor.

3. Mental symptoms are almost twice as frequent in patients with supratentorial as in those with infratentorial tumor of the brain.

4. Disturbances in memory are predominantly more frequent in individuals with supratentorial tumor than in those with infratentorial tumor.

5. Complex visual and auditory hallucinations are more frequent in patients with tumor of the temporal lobe.

6. Crude auditory hallucinations are heard by the patients most commonly on the side of the tumor, whether the tumor is located above or below the tentorium.

7. Localized tactile hallucinations indicate that the parietal lobe opposite to the side of the hallucination is the seat of the tumor.

8. The most severe and most varied type of psychic disturbances are observed in patients in whom the tumor involves both sides of the brain.

9. Psychogenic reactions are determined more frequently by physical or by subjective disabilities and by the total personality of the individual rather than by the location of the tumor in any one part of the brain.

10. The pathogenic factors in the production of mental symptoms, in the order of their importance, are (*a*) involvement of both sides of the brain, (*b*) increased rate of development of symptoms of tumor of the brain in general, (*c*) the rapidity of the tumor growth, (*d*) sudden appearance and rapid development of intracranial hypertension and (*e*) supratentorial location of the tumor.

11. The age, general condition and premorbid personality of the patient modify the quality of the mental reactions to physical symptoms.

THE TESTING OF ACTIVITY OF CHILDHOOD TUBERCULOSIS

RELATIVE VALUE OF THE SCHILLING DIFFERENTIAL COUNT, THE SEDIMENTATION RATE AND THE LYMPHOCYTE-MONOCYTE RATIO

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The frequent use of the intracutaneous tuberculin test has done much in bringing to light early childhood tuberculosis. Even with a history of exposure and x-ray evidence it is difficult to decide whether the tuberculous infection is active. Reliance on clinical courses is often not sufficient.

In the past few years many excellent reports have shown certain laboratory aids to be of great prognostic value for adults with tuberculosis. On the other hand little such data have been presented relative to childhood tuberculosis, the best reports being concerned with the number of lymphocytes and monocytes. Any simple tests that would throw light on the activity of tuberculosis in childhood or on its prognosis would be of great value.

Through the cooperation of Drs. W. E. Brown, Frank B. Stafford and E. C. Cole of Blue Ridge Sanatorium, Charlottesville, Va., a study of the relative value of the Schilling differential blood count, the sedimentation rate and the lymphocyte-monocyte ratio was made on forty children over a period of approximately six months. The sedimentation rate and the total cell counts were determined by a trained technician at the sanatorium, and the Schilling differential count and the lymphocyte-monocyte ratio were determined by me in another city. The supravital staining

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was not used in studying the monocytes. Friedman and his associates [1] did not find any great difference between lymphocyte-monocyte ratios obtained by the ordinary stain and by the supravital method and considered the former much simpler and more practical. At various times the physical and clinical data found by Drs. Brown, Stafford and Cole were compared with the laboratory data. I feel that the study, even though of short duration and concerned with so few children, is of sufficient interest to report.

TABLE 1.—*The Relative Value of the Schilling Differential Blood Count, the Sedimentation Rate and the Lymphocyte-Monocyte Ratio in Testing the Activity of the Tuberculosis of Childhood*

1. The Schilling Differential Blood Count

The greater the percentage of immature neutrophils present, the more severe the infection or damage to tissue. The division of the immature neutrophils (myelocytes plus juveniles plus stabs) by the total neutrophils (myelocytes plus juveniles plus stabs plus segments) gives the percentage of immaturity, or the so-called shift to the left percentage.

Normal	Slight Infection	Moderate Infection	Severe Infection	Very Severe Infection
4-15%	16-30%	31-50%	51-70%	71% or greater

2. The Sedimentation Rate

The distance in which citrated red blood cells settle in a certain size small tube in a given period represents the injury to the red cells from an infection or change in tissue. The more rapid the rate, the more severe the infection or derangement of tissue.

Normal	Slight Infection	Moderate Infection	Severe Infection	Very Severe Infection
0-10 mm.	11-15 mm.	16-25 mm.	26-30 mm.	31 mm. or greater

3. The Lymphocyte-Monocyte Ratio

An increase in the number of lymphocytes with a normal percentage of monocytes represents the tendency to healing, and, conversely, a low lymphocytic and a high monocytic percentage suggest a more severe infection and a greater tendency to extension of the infectious process.

It is common knowledge that at autopsy one finds in a single case lesions of all stages. By studying all leukocytes in the circulating blood, one can get a good mental picture of the pathologic changes taking place. Such a study must of course be undertaken under similar conditions and at regular intervals, and the differential count had best be done by the same person to get optimum results.

The tuberculosis of the children in the series was classified as suspicious, minimal, moderately advanced and far advanced.

The brunt of the attack against the tubercle bacillus in all of its stages is borne by the monocytes; the neutrophils and the lymphocytes appear to be adjuvants only. Sabin [2] and Blackfan [3] have found the monocyte to be concerned with the spread of the disease and with the formation of new tubercles. The damage to tissue resulting from the monocyte-tubercle bacillus fight causes stimulation of the bone marrow, which in turn gives rise to cellular changes in the circulating blood.

A consideration of the percentage of immature neutrophils in relation to the mature polymorphonuclears gives an excellent idea of the severity of an acute infection in childhood.[4] Normally about 5 to 15 per cent of neutrophils are immature, while in infections that percentage increases. In an infection of slight severity one finds about 16 to 30 per cent, in a moderate infection about 31 to 51 per cent and in a very severe infection from 51 to 70 per cent, while a percentage of over 70 for a prolonged period is suggestive of impending death. The appearance of the nucleus and its cytoplasm also aids in determining toxicity; [5] when the nucleus is greatly distorted and the cytoplasm filled with deeply stained granules, one is dealing with a very severe infection.

The percentage immaturity of neutrophils, or the so-called shift to the left, in this small series was in keeping with the interpretation just mentioned. A shift of from 20 to 40 per cent was finally found for the group with tuberculosis classified as suspicious or minimal. In the cases of moderately advanced tuberculosis a percentage of from 25 to 40 was generally seen, while in the cases of far advanced infection the immaturity was in the neighborhood of from 50 to 80 per cent. Only in the last named group were toxic granules noted. Occasionally the shift was out of keeping with the clinical classification; such shifts were felt to represent a truer picture of the manner in which the child is handling his tuberculous infection than x-ray or clinical evidence. This is in agreement with Flinn.[6]

The rapidity of the sedimentation rate gives some measure of the intensity of an infection or derangement of tissue. A series of such rates should give prognostic information. The normal sedimentation rate within one hour is considered to be ten millimeters or less.[7] In the cases of minimal activity in this series the rate was within the normal range or occasionally as high as fifteen millimeters. When there was moderately advanced tuberculosis a rate of from fifteen to twenty millimeters was noted, and in the cases of far advanced infection a rate of more than twenty millimeters was usually observed. While it is realized that anemia itself will

TABLE 2.—*The Schilling Differential Blood Count for W. B., Aged 9 Years, Who Had Tuberculosis Classified as Suspicious*

Date	Basophils	Eosinophils	Myelocytes	Juveniles	Stabs	Segments	Lymphocytes	Monocytes	Shift, Percentage	Comment
12/14/32	0	4	0	0	10	31	51	4	24	Old tuberculin test positive, 0.01 mg.
1/ 2/33	0	8	0	1	5	33	50	3	15	
1/18/33	0	9	0	0	10	39	36	6	21	
2/ 2/33	0	4	0	0	16	32	44	4	33	
2/15/33	0	7	0	1	17	27	42	6	40	
2/28/33	0	9	0	0	8	35	44	4	19	
3/16/33	1	11	0	0	18	23	51	6	35	Asthma
4/ 4/33	1	10	0	1	10	27	44	7	29	Asthma
5/ 8/33	1	8	0	0	4	36	49	2	10	Improved

Comment.—The first count is in agreement with the classification so far as the severity of the infection is concerned. At the time of discharge the blood picture showed a normal shift and a normal percentage of monocytes, with increased lymphocytes. The sedimentation rates were 5 mm., 4 mm., 9 mm. and, at discharge, 8 mm. On May 8 the infection had become inactive, and healing had occurred.

1. Friedman, Eli; Dameshek, William, and Hawes, John B. 2d: The Examination of the Blood as an Aid in the Diagnosis of Hilum Lymph Node Tuberculosis, Am. Rev. Tuberc. **25**: 24-31 (Jan.) 1932.
2. Cunningham, R. S.; Sabin, F. R.; Sugiyama, S., and Kindwall, J. A.: Role of the Monocyte in Tuberculosis, Bull. Johns Hopkins Hosp. **37**: 231 (Oct.) 1925.
3. Blackfan, K. D., and Diamond, L. K.: The Monocyte in Active Tuberculosis, Am. J. Dis. Child. **37**: 233-234 (Feb.) 1929.
4. McGee, W. Ambrose: The Value of the Schilling Differential Blood Count in Pediatrics, South. M. J. **25**: 484-489 (May) 1932.
5. McGee, W. Ambrose: The Importance of Immature White Blood Cells in Diseases of Children, South. M. J. **28**: 43-46 (Jan.) 1935.
6. Flinn, John W., and Flinn, Robert S.: The Leukocytic Picture of the Blood as an Aid in the Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **20**: 347-357 (Sept.) 1929.
7. Cutler, J. W.: The Practical Application of the Blood Sedimentation Test in General Medicine, Am. J. M. Sc. **183**: 643-659 (May) 1932.

give rise to an abnormal sedimentation rate, I feel that an attempt to correct the rate for the anemia [8] is not advisable, as the anemia is part of the clinical course.

In a few instances, as with the Schilling differential count, the sedimentation rates did not parallel the clinical course of the tuberculosis. In such instances it is felt that it is better to rely on the change in the sedimentation rate than on clinical impression.

TABLE 3.—*The Schilling Differential Blood Count for M. G., Aged 11 Years, Who Had Tuberculosis Classified as Minimal*

Date	Basophils	Eosinophils	Myelocytes	Juveniles	Stabs	Segments	Lymphocytes	Monocytes	Shift, Percentage	Comment
12/14/32	0	4	0	2	18	27	44	5	43	Test with old tuberculin positive, 0.01 mg.
1/ 6/33	0	0	0	1	12	39	44	4	25	
1/19/33	1	6	0	3	18	39	36	7	42	
2/ 2/33	1	2	0	2	9	41	35	10	21	
2/15/33	2	5	0	0	8	31	43	11	22	
2/28/33	0	6	0	0	10	49	33	2	18	
3/17/33	1	4	0	3	18	30	39	5	41	
4/ 8/33	0	4	0	2	17	35	34	8	35	
5/ 6/33	0	4	0	0	17	37	31	11	31	
11/29/33	0	1	0	0	18	41	36	4	13	Improved

Comment.—The first count is in agreement with the classification so far as the severity of the infection is concerned. At the time of the last count the shift was normal, the percentage of lymphocytes slightly increased and the percentage of monocytes normal. The sedimentation rates were 13 mm., 9 mm., 13 mm. and 4 mm. On November 29 the infection was nonactive, and healing was taking place.

Much information has been presented in the study of the lymphocytes and monocytes. It has been shown by many writers that if the number of monocytes is high new tubercles are forming, and that if it is normal or low and there is a gradual increase in the percentage of lymphocytes healing is taking place. In this study the number of monocytes was found to fluctuate so greatly that it was difficult to form any definite opinion. In cases of minimal tuberculosis it was usual to find the monocyte count between 2 and 9 per cent; in cases of moderately advanced infection, between 4 and 10 per cent, and in cases of far advanced infection, between 7 and 15 per cent, usually above 10 per cent. When patients were improving clinically the monocytes were generally below 8 per cent, while the lymphocytes were in the neighborhood of 40 per cent or more and the immature neutrophils were less than 30 per cent.

TABLE 4.—*The Schilling Differential Blood Count for B. W., Aged 9 Years, Who Had Tuberculosis Classified as Moderately Advanced*

Date	Basophils	Eosinophils	Myelocytes	Juveniles	Stabs	Segments	Lymphocytes	Monocytes	Shift, Percentage	Comment
2/ 2/33	0	0	0	14	27	10	35	14	80	Test with old tuberculin positive, 0.02 mg.
2/15/33	1	2	0	11	40	15	22	9	73	
3/ 9/33	0	0	0	3	40	14	30	13	76	
3/17/33	0	4	0	3	48	8	36	1	86	
4/ 4/33	0	1	0	8	46	8	26	11	87	
5/ 6/33	0	1	0	10	52	11	16	10	85	
12/13/33	0	2	0	3	36	20	34	5	66	Slightly improved

Comment.—All counts showed evidence of a far advanced or very toxic type of infection. The shift remained extremely high, the percentage of lymphocytes was very low and the percentage of monocytes was usually high. The sedimentation rates were 34 mm., 36 mm., 35 mm. and 31 mm. The laboratory data disagreed with the clinical classification. The patient subsequently died.

In childhood the number of lymphocytes is normally so high that it is more difficult to get information than in cases of adult tuberculosis; so in studying the percentage of lymphocytes one has to have in mind what is to be expected for the age of the child in question.

In ordinary acute infections of childhood a sudden rise in monocytes usually foretells the dawn of convalescence.[9] This is not true in tuberculosis. Likewise when there are four times more lymphocytes than monocytes, provided the latter are present in normal numbers, healing is apt to be taking place. No such impression could be derived from the ratio between lymphocytes and monocytes in this study. However, for the patients with far advanced tuberculosis who were not improving clinically, as well as for private patients with miliary tuberculosis, it was usual to find a very low lymphocytic percentage with a very high monocytic one. The ratio then was about one to one, which would indicate, so far as the lymphocyte-monocyte ratio is concerned, absolute absence of healing.

TABLE 5.—*The Schilling Differential Blood Count for E. C., Aged 11 Years, Who Had Tuberculosis Classified as Far Advanced*

Date	Basophils	Eosinophils	Myelocytes	Juveniles	Stabs	Segments	Lymphocytes	Monocytes	Shift, Percentage	Comment
1/19/33	1	2	0	10	16	34	37	10	44	Positive sputum
2/ 2/33	0	3	0	4	22	30	35	6	46	
2/15/33	0	0	0	5	27	31	25	12	51	
2/28/33	0	3	0	1	41	29	22	4	58	Pneumothorax
3/16/33	0	5	0	6	34	21	22	12	66	
4/ 7/33	2	2	0	1	24	30	28	13	45	
5/11/33	0	2	0	1	27	37	25	8	43	Pneumonolysis
12/ 9/33	2	1	0	3	25	42	23	4	37	Improved

Comment.—The shift in most instances represents a less severe infection than a far advanced type of tuberculosis. The high shift and the high percentage of monocytes indicate new tubercle formation with suppuration. The relatively low percentage of lymphocytes is in keeping with little or no healing. In the last count improvement is seen, with some slight suggestion of healing. The sedimentation rates were 28 mm., 31 mm., 30 mm. and 39 mm. The sedimentation rates as a whole disagreed with the shift and the clinical improvement.

Total white cell counts were not obtained with each weekly or bimonthly blood smear, but, when done, the counts were usually well within the normal range except in the cases in which the infection was far advanced or another infection was superimposed. It was usual to find a white cell count of from 5,000 to 7,500 in the cases of minimal tuberculosis. A study of the size of the different white cells with a micrometer was time consuming and proved of no practical value.

COMMENT

1. A study of the cells in the circulation at regular intervals and under similar conditions by the same person gives a mental picture of the pathologic changes occurring.

8. Walton, A. C. R.: The Corrected Erythrocyte Sedimentation Test, J. Lab. & Clin. Med. **18**: 711-723 (April) 1933.

9. Gradwohl, R. B. H.: The Schilling Blood Methods, Long Island M. J. **24**: 261 (May) 1930.

2. The laboratory data per se do not in any way suggest the kind of infectious agent, for red and white cells respond only to the type of damage done to the tissues.

3. Total white cell counts per se are of relatively little or no prognostic value but when considered from

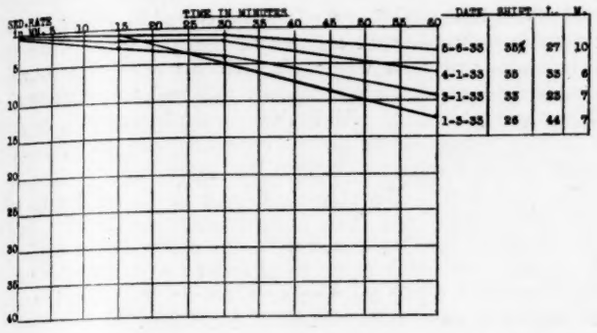


Chart 1.—Sedimentation rates for S. B., aged 13, with tuberculosis classified as suspicious. In this and the accompanying charts the horizontal line indicates from normal activity to quiescence, the diagonal line from quiescence to slight activity, the diagonal curve from slight to moderate activity and the vertical curve from moderate to marked activity. The sedimentation rates shown in this chart agree with the clinical classification, but all except the first are normal, whereas the shift shows evidence of slight activity throughout. The percentage of monocytes is relatively high and the percentage of lymphocytes nearly normal for age.

the standpoint of total neutrophils, lymphocytes and monocytes are of value.[10]

4. Through a consideration of the maturity of the neutrophils or the sedimentation rate, the best prognostic information is obtained.

5. Any definite lymphocyte-monocyte ratio was unobtainable because of the great fluctuation in the monocytic percentages. However, a normal monocyte count with an elevated lymphocyte count indicates healing, whereas, the reverse ratio suggests extension of the tuberculous infection.

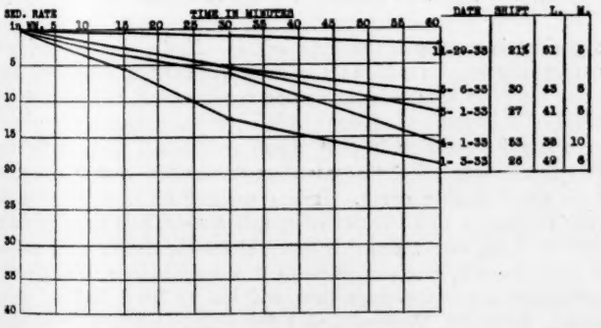


Chart 2.—Sedimentation rates for B. J. C., aged 9 years, with tuberculosis classified as minimal. The first sedimentation rate, shift, percentage of lymphocytes and percentage of monocytes are in agreement with the clinical classification. The last sedimentation rate, shift and percentage of monocytes are normal, while the percentage of lymphocytes is high, indicating inactivity of infection, with good healing.

6. When clinical courses do not parallel laboratory data, especially the shifts and the sedimentation rates, it is advisable to pay more attention to those two tests.

7. Evidence of relapse or retrogression is first noted in the Schilling shift days or weeks prior to roentgenographic or physical evidence.

8. A continuous septic type of blood picture is more suggestive of extension of the pathologic process, and there is danger of hemorrhage.

10. Medlar, E. M.: An Evaluation of the Leukocytic Reaction in the Blood as Found in Cases of Tuberculosis, Am. Rev. Tuberc. **20**: 312-346 (Sept.) 1929.

9. The blood picture indicates the status of the infection only at the time the blood is obtained for study.

SUMMARY

1. It is possible and practical from a study of the blood under regular conditions to secure reasonably reliable prognostic information.

2. Greater prognostic aid is obtained from the shift and the sedimentation rate than from the lymphocyte-monocyte ratio per se.

3. Earlier pathologic changes are shown by the shift.

4. In cases of moderately or far advanced tuberculosis the shift and the sedimentation rate more or less parallel each other. When the tuberculous infection is slight the shift is usually slightly elevated while the sedimentation rate is generally normal.

5. The Schilling count or a modification of it is more practical for children and has many advantages over the sedimentation test. Some of the outstanding points in favor of the Schilling differential count are as follows:

(*a*) Less blood is required.

(*b*) Children have much less fear of finger pricks than of venous punctures.

(*c*) All kinds of blood cells can be studied in a stained smear.

(*d*) Less time is required.

(*e*) Differential counts can be made days after a slide is stained.

(*f*) Stained smears can be kept as a semipermanent record.

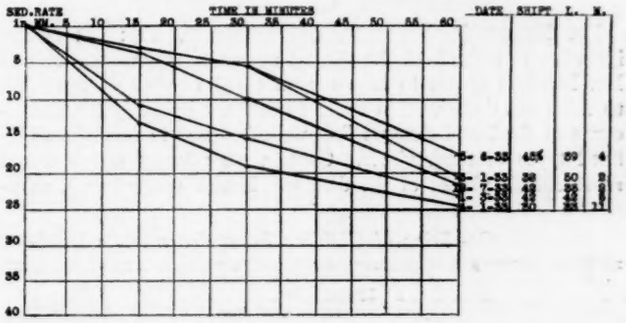


Chart 3.—Sedimentation rates for D. G., aged 15, with tuberculosis classified as moderately advanced. The sedimentation rate and the shift, as well as the percentage of lymphocytes and of monocytes, are in agreement with the clinical classification. The last sedimentation rate and shift indicate only slight improvement. The percentage of lymphocytes is relatively high and the percentage of monocytes normal, suggesting healing and no new tubercle formation; they disagree with the shift and the sedimentation rate.

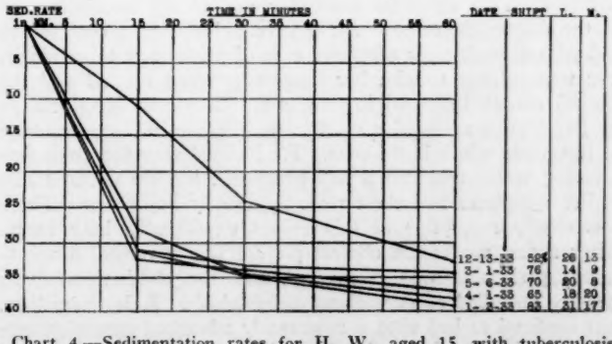


Chart 4.—Sedimentation rates for H. W., aged 15, with tuberculosis classified as far advanced. The sedimentation rate, shift, percentage of lymphocytes and percentage of monocytes agree with the clinical classification. There was relatively no improvement during the entire course of the study. These data are in keeping with the clinical course.

(*g*) Evidence of slight flare-ups and superimposed infections are detected much more quickly and consistently.

6. More detailed cellular structure is visible with the use of Giemsa's stain than with Wright's stain.

7. A combination of the shift percentage and the progressive changes in the percentage of lymphocytes and monocytes gives the optimum prognostic information. Such a combination also gives a clearer idea of the extent of the infection.

8. Laboratory tests should in no way be used to replace clinical and roentgen examinations but should be used regularly in conjunction with them.

1601 Monument Avenue.

ABSTRACT OF DISCUSSION

DR. FRANK B. STAFFORD, Charlottesville, Va.: It is my intention to talk about the clinical aspect of this work. It was Dr. McGee's object to take only a small number of cases but to work out these well in order to evaluate properly the significance of the blood changes that were believed to occur in childhood types of tuberculosis. Cases were selected which would represent all phases of the disease. Latent (suggestive), minimal, moderately advanced and far advanced groups were included. Special attention was given to the clinical course of the patients during the period this work was under way in order to determine what variations, if any, existed. From previous work by Dr. McGee it was believed that it would prove valuable from the standpoint of diagnosis of severity and prognosis in tuberculous children. These two claims were fully justified. Two cases in particular are worth mentioning as to the diagnostic value: An 8 year old girl was confined to bed with a moderately advanced case of pulmonary tuberculosis. She was gaining weight, her temperature was normal and the clinical course indicated improvement. Repeated blood counts by Dr. McGee revealed a continuous increase in the percentage of immature white blood cells. He insisted that the child was growing worse and had a bad prognosis, but we doubted this as her symptoms and chest were apparently improving. There was steady resorption of tuberculous exudates in both lungs. After a few weeks the clinical picture was reversed, a tuberculous peritonitis was discovered, and the child went down steadily and died of generalized tuberculosis. A boy, aged 16, was confined to bed with a moderately advanced case of tuberculosis and had tubercle bacilli in his sputum. His fever had subsided, he was gaining weight steadily and otherwise seemed to be improving. The Schilling count revealed an increasing shift to the left, and the red cell sedimentation rate showed a steady drop. A roentgenogram of the chest revealed a spread of disease in the left lung with formation of an excavation. Permission was then given by the parents for artificial pneumothorax, but a continuous extension of the disease in the contralateral lung made the compression unsuccessful and the boy died of fulminating pulmonary tuberculosis. Both of these cases show that the Schilling blood count and red cell sedimentation rate in tuberculous children may reveal a spread of the disease weeks before it can be detected by the clinical course. It also seems to have a dependable prognostic value. Four years after discharge from the sanatorium an attempt was made to locate the children on whom this blood work was done to see what their condition was. A study of the accompanying table shows that a report was obtained in 86.5 per cent of the cases and that death had occurred in 60 per cent of the moderately advanced and far advanced cases in which an unfavorable prognosis was made. Of the remaining patients located, 96.3 per cent are apparently well and are either working or going to school. All but two in the latter group carried a good prognosis from the sedimentation rate and Schilling counts which were done on them four years ago.

DR. J. I. LINDE, New Haven, Conn.: I should like to ask whether this is of any value in prognosticating the advance in the tuberculin-positive contacts. I am conducting a study in Negro children and it might be of interest to know whether a Schilling count would be of value in determining what is going to happen to these tuberculin-positive children.

DR. W. AMBROSE McGEE, Richmond, Va.: I cannot answer this question positively, but from the study of the Schilling blood count in nontuberculous cases I can state that the procedure usually gives a good deal of information as to whether a patient is getting better or slipping. If the same technician who performs this follows the same patients at relatively the same intervals and under the same conditions, it will give quite a bit of information. I don't think the sedimentation test will give any information in that stage, and, again, I want to say that in children I feel that a sedimentation test cannot compare with the Schilling count. It has nothing to offer (except in rare instances) that the Schilling will not do, and the Schilling will give all one needs. If one pricks the finger and stains it soon enough, one can refer to it a month later. The sedimentation test takes more time and has to be looked at right away. Both Dr. Stafford and I feel that, while the study was of short duration and represented very few children, it is in keeping with the results in acute infections. There is no reason why it should not be of some value to give one an idea of severity or to give one an idea of the prognosis of the particular child in question.

Condition of Children Four Years After Discharge, Showing Prognostic Value of Blood Examination

Class	Number of Children	Percentage of Immature Neutrophils	Sedimentation Rate in One Hour	History of Contact	Tuberculin		Condition on Discharge				Condition Four Years After Discharge				
					Positive	Negative	Improved	Unimproved	Quiescent	Dead	Number Located	Well Working	Well At School	Relapsed	Dead
Suggestive or latent	23	20-40	0-10	19 (83%)	17 (74%)	6	23	0	0	0	18	6	12	0	0
Minimal	9	20-40	10-15	9 (100%)	9 (100%)	0	5	1	3	0	9	3	5	1	0
Moderately advanced	8	25-50	15-20	3 (100%)	3 (100%)	0	0	0	2	1	3	0	2	0	1
Far advanced	2	50-80	20-60	2 (100%)	2 (100%)	0	0	1	0	1	2	0	0	0	2

One child with moderately advanced tuberculosis and one with far advanced tuberculosis died in the sanatorium; the other child with far advanced tuberculosis died soon after discharge. Thus 60 per cent of the children with moderate and far advanced tuberculosis are dead. Of the remaining twenty-seven children located, twenty-six, or 96.3 per cent, are apparently well and either working or going to school.

Time-Lag in Medicine.—The recognition of *vitamins* is a more recent story. But here the time-lag between the realization of an error in dietary in such diseases as scurvy, beriberi and rickets and the discovery of the actual cause was a much longer one, particularly in the case of scurvy, where the curative effect of lemon juice had been known since the seventeenth century. The long dispute as to whether rickets was a disease of the dark or of diet was at last resolved in a manner satisfactory to both parties when the influence of ultraviolet rays on the production of vitamin D was demonstrated.—Langdon-Brown, Walter: The Dead Hand in Medical Science, *Lancet* **1**:379 (Jan. 29) 1938.

AUDIOMETERS AND HEARING AIDS

AUSTIN A. HAYDEN, M.D.
CHICAGO

For the practicing otologist the audiometer [1] is an electrical instrument for measuring hearing in the physician's office. Direct or alternating current may be used. It measures loss of hearing in decibels (db) at calibrated frequencies (pitch) and supplants the old methods, in which the voice, watch, acumeter, tuning forks, rods, bells and whistles were used. The examiner may now increase, decrease or hold stationary the intensity of any frequency on the audiometer for any length of time desired. The decay of the tuning fork always limited its usefulness and was outstanding among the errors inherent in the old methods.

The full hearing range, as it has been taught, from 20 to 20,000 cycles per second, for which former testing equipment was manufactured, is not covered in its entirety by any audiometer exhibited at this meeting. This is largely because of excessive manufacturing costs and doubtful clinical utility. However, the older instruments of precision can and should be used when necessity arises or comparisons are desired.

In general the results of tests with the audiometer are plotted so that frequency runs horizontally across the chart from 64 to 8,192 or over and is calibrated in octaves, half octaves and/or octave letters. Sweeps cover all or part of the octave calibrations and go far beyond these pitches, to as high as 16,000 cycles per second. Intensity is measured in decibels between the threshold of audibility and of pain and is charted vertically. The ordinary telephone receiver transforms the electrical energy of the audiometer into sound cycles for air conduction through the external auditory canal. For bone conduction through the mastoid, a specially constructed receiver is provided.

Additional equipment now available includes maskers, microphone amplifiers for speech articulation tests, plans and specifications for soundproof rooms, rubber receiver cups for use where such rooms are not practical and specially prepared charts.

HEARING AIDS

Electrical hearing aids raise the sound level for transmission by air through the external auditory canal to the drum and by bone—thanks to Lieber for the bone conduction receiver—through the mastoid to the inner ear. They are portable, semiportable and stationary. The first uses small single or multiple dry cells, the second either large dry cells or line current or both, and the last line current only. This paper deals only with the portable aids because they are the most widely used.

Portables are amplified or nonamplified. They are specially adapted telephone hook-ups, consisting essentially of a receiver (ear piece), transmitter (microphone) and battery. In the amplified set an amplifier, or booster, with its second circuit, is added. Cells may number from one to four, and the battery delivers from 1½ to 6 volts. Too few or worn out cells prevent sufficient amplification.

The frequency range of portables lies principally from 256 to 2,000 cycles per second, where most conversational tones come. Some amplification is possible as high as 3,500 or 4,000 cycles per second. By altering the construction of the transmitter the sound can be "peaked" at one or more frequencies; by changing the characteristics of the receiver another "peak" is obtained. Thus sound may be "peaked," or intensified, effectively within three divisions (low, middle and high) to fit approximately the loss of hearing shown on an audiogram. Amplification can also be spread out evenly over a fairly broad area. Thus the electrical and mechanical characteristics of the transmitter, receiver and booster, when used in various combinations, afford literally hundreds of different hearing aids. How many are actually practical is an open question.

RESPONSE CURVES OF HEARING AIDS; AUDIOGRAMS OF HEARING AIDS; MASTER HEARING AIDS

By passing the audiometer's calibrated tones into the hearing aid's transmitter and measuring the output with a decibel meter, the over-all "tone characteristics" of the various arrangements of component parts can be plotted into "response curves" of the hearing aid. The actual change the hearing aid makes in the patient's hearing can be ascertained by attaching the audiometer's ear piece to the transmitter of the patient's hearing aid and charting the audiometer reading of the patient in the usual way. When plotted on the patient's original audiogram, a graphic picture of the hearing before and after fitting is immediately exhibited. This is the audiogram of the hearing aid which will be considered in a subsequent paper.

The audiometer may be compared to the retinoscope. The latter determines both degree and position of errors of refraction. The former locates both position (frequency) and degree (intensity) of loss of hearing. "Tone islands" correspond roughly to astigmatic errors of refraction and indicate the position (frequency-pitch) [2] at which the intensity (loudness) of the hearing aid should be "peaked." Just as the trial frame enables the patient to look through the various lens combinations indicated by the retinoscope, likewise the deafened patient can actually hear through the half dozen combinations indicated by the otologist's audiogram. Carefully worked out [3] speech articulation tests determine the combination best suited to the individual requirements.

This great improvement in fitting has been effected by the development of what, for want of a better generic name, may be called the master hearing aid. All but one of the four largest manufacturers fit from the results of tests with this instrument. The excepted firm uses audiograms only, which are made in its own sales rooms. It audiometric analysis is advertised to be for the fitting of hearing aids only and not for the diagnosis of ear disease. Two firms consider audiograms unnecessary and depend entirely on master hearing aids to make their fittings. The fourth uses its

This work was facilitated by an expense grant from Sonotone Corporation.

Clinical material was obtained from private practice, the Chicago League for the Hard of Hearing and the outpatient department of St. Joseph's Hospital.

Read before the Annual Meeting of the American Academy of Ophthalmology and Oto-Laryngology, Chicago, in October 1937, and in part before the Chicago Laryngological and Otological Society.

1. "A clinical audiometer is an instrument for measuring the acuity and range of hearing." Tentative Minimum Requirements for Acceptable Audiometers, Report of the Council on Physical Therapy, J. A. M. A. **109:** 1812 (Nov. 27) 1937.

2. Pitch is that subjective quality of a sound which determines its position in a musical scale. Loudness is that subjective quality of a sound which determines the magnitude of an auditory sensation produced by that sound. American Standards Association, Bulletin of Acoustic Terminology, Oct. 15, 1936.

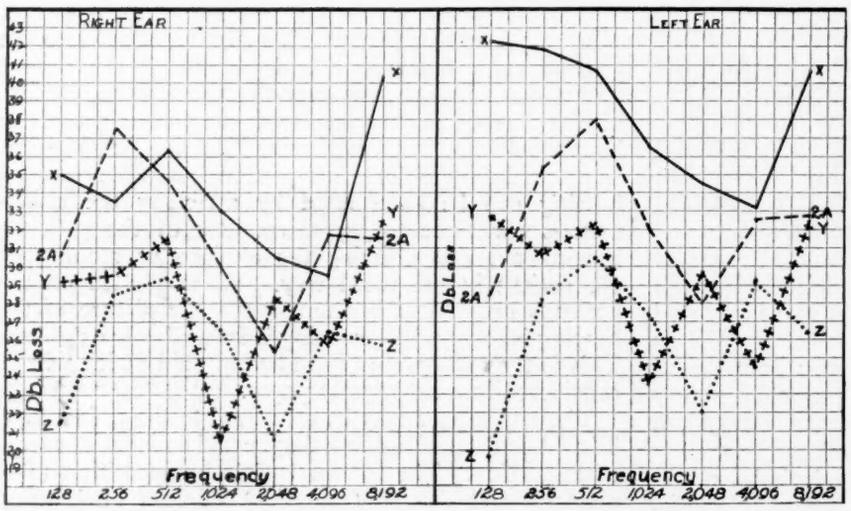
3. The need of speech articulation tests is well treated in Ewing, A. W. G.; Ewing, I. R., and Littler, T. S.: Reports of the Committee upon the Physiology of Hearing: IV. The Use of Hearing Aids, Special Report Series, No. 219, London, His Majesty's Stat. Off., 1936.

own master hearing aid in addition to an otologist's audiogram, which it believes to be essential.

Just how the vacuum tube works in the audiometer, how sound is amplified, how the attenuator sweeps the entire intensity range between the threshold of hearing and that of pain, how to define bel and decibel and how to comprehend sound in terms of drum surface pressure require highly technical knowledge. The hearing aid presents similar problems. Otologists may well leave such matters to the Bureau of Standards, the American Standards Association, the American Medical Association's Council on Physical Therapy and the professional associates and designated consultants of these bodies.

TESTS OF AUDIOMETERS

As unnecessary minimum requirements increase the cost and thereby, to some extent, limit the use of any apparatus designed for wide clinical use, it is desirable to determine the value of such requirements. In audiometers pure wave form, which does add greatly to construction costs, has been considered necessary, especially by laboratory workers. To determine its real value in actual practice, thirty persons who were moderately hard of hearing were tested with four audiometers. Three of these, X (Sonotone), Z (Western Electric 6-A) and Western Electric 2-A, probably meet the requirements of the Council on Physical Therapy, while Y (Marvel) has an admittedly imperfect wave form. Western Electric 2-A was arbitrarily taken as a standard for comparison because of its long established (but unfortunately far from sufficient) use and the literature it has created.



Curves showing the average loss of hearing of sixteen persons as measured by four different audiometers (896 observations). *X* indicates the Sonotone audiometer, *Y* the Marvel, *Z* the Western Electric 6-A, and *2-A* the Western Electric 2-A. Intensity (loudness) is plotted vertically in decibels and frequency (pitch) horizontally at octave intervals. Tests at octave letters, as well as sweeps, through the conversation range (from 256 to 2,048) would probably have revealed the existence of many tone islands. The figure 896 is obtained by multiplying 4 (audiometers) by 7 (frequencies) by 2 (ears) by 16 (patients). As each observation averaged a minimum of three readings, the individual observations actually total more than 2,588.

The four audiometers were placed in a small inside room of an otologist's office. The doors and windows in this and the adjoining outside rooms were closed during the tests. The average noise level was then reduced from 50 to 20 decibels. A thick rubber hood around the air receiver, with a similar cup over the opposite ear, further lowered the noise level but to exactly what extent was not determined.

Audiometer X is provided with dials for octave (from 128 to 8,192) as well as sweep frequencies (from 2,500 to 17,000). Intensity is calibrated in steps of 5 decibels. It is provided with an automatic self-compensating pointer. Audiometer Y has an octave, octave letter and sweep frequency range from 64 to 8,192, with attenuation from 0 to 100 decibels at all frequencies. Audiometer Z has two dials, one for sweep frequency marked with eight indicated points from 128 to 9,847. For bone conduction tests, a ring is placed over the intensity dial for recalibration.

When being tested, the patient responded by the usual finger or electric signal. The average of a minimum of three readings based on air conduction at each of the octave frequencies was taken to be the actual loss of hearing and charted as such on the individual audiograms and recorded. These three readings almost never varied from each other by more than plus or minus 5 decibels. The tests were made by three experienced observers. Rest periods were used as needed to minimize the confusion due to fatigue of both the patient and the observer.

Fourteen of the thirty patients were found to have losses of hearing greater than the Western Electric 2-A audiometer could measure. For that reason their audiograms were discarded. The losses of the remaining sixteen, as shown by each of the four audiometers, were averaged and plotted. Differences between the readings at most frequencies are apparent on the chart. The average difference for all frequencies is readily compiled and is not great.

SUMMARY

1. Four audiometers of different makes were investigated to determine their comparative performances for air conduction tests [4] and the need for pure wave form in clinical practice.

2. Audiometer X consistently showed the highest loss of hearing, Y showed a medium but more erratic loss and Z showed the smallest loss. As compared with the 2-A audiometer the average differences were plus 5 decibels for X, minus 3 decibels for Y and minus 6 decibels for Z.

3. Audiometers X, Y and Z were capable of measuring greater losses of hearing than 2-A.

4. Plus or minus 5 decibels was found to be the combined human error factor of observer and patient.

5. An average quiet, not soundproof, room was used for the tests.

CONCLUSIONS

1. Audiometers, despite the foregoing variations, furnish the best means of testing hearing acuity.

2. Any one of the four tested will be more useful in clinical practice than any other means now available for testing and recording hearing acuity.

3. The lack of purity of sound wave apparently did not introduce any serious errors that were not largely explainable by other causes.

4. A quiet room is essential. The need for a soundproof room increases as the loss of hearing to be tested decreases.

5. An audiometer should be part of the office equipment of every otologist.

4. Comparisons for bone conduction will subsequently be reported.

OTOLOGIST'S COMMITTEE

Through the Otologists' Committee on Audiometers and Hearing Aids,[5] the Council on Physical Therapy of the American Medical Association places its facilities at the disposal of otologists for the purpose of correlating clinical experience, laboratory procedure and manufacturing detail. Acceptance by this Council should become an incentive to manufacturers to construct instruments in accordance with agreed-on clinical requirements and should assure otologists that advertised claims meet required specifications.

25 East Washington Street.

Clinical Notes, Suggestions and New Instruments

THROMBOCYTOPENIC PURPURA FOLLOWING ALLYL-ISOPROPYL-ACETYL-CARBAMIDE (SEDORMID)

ARTHUR M. HOFFMAN, M.D.; JULIUS KAHN, M.D., AND J. P. FITZGIBBON, M.D., LOS ANGELES

The purpuric state has been classified by Leschke [1] and modified by Pratt [2] into the nonthrombocytopenic and the thrombocytopenic varieties. Of the latter, Werlhof's disease or essential thrombocytopenic purpura forms the larger group with the secondary or symptomatic thrombocytopenic purpura due to x-rays, radium, leukemia, benzene and arsphenamine comprising the remainder.

The etiology of purpura being manifold, further description of apparently authentic etiologic agents is justified.

Squier and Madison's [3] description of three patients in whom definite thrombocytopenic purpura seemed related to food allergy is an example of this trend. Quinine sensitivity producing thrombocytopenia and purpura has been described by Maritschek and Markowicz [4] and by Peshkin and Miller [5] for quinine and ergot.

Sedormid (allyl-isopropyl-acetyl-carbamide) was first reported as suspect as an etiologic agent in thrombocytopenic purpura by Loewy [6] in 1934. In one patient severe purpura with thrombocytopenia could be induced at will by the administration of a one-half to one-fourth grain (0.032 to 0.016 Gm.) tablet of the drug. This patient had taken sedormid previously for almost a year without untoward manifestations. Two other milder cases are described. In 1933 Dennig [7] reported a case in a woman with purpura and ascribed it to the ingestion of iodine, with two subsequent recurrences, each one the day following administration of sedormid. In a foreign letter of THE JOURNAL appeared a description of two cases presented by A. Vogel [8] to the Vienna Medical Society. Both patients had taken sedormid on occasions without untoward effect and both had had long intervals between taking the drug. On two later occasions severe purpura with marked thrombocytopenia developed.

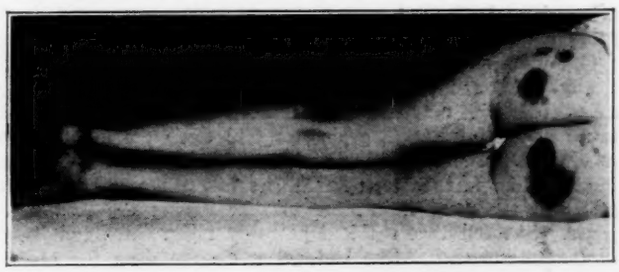
Boas and Erf [9] recently reported another instance of thrombocytopenic purpura following the ingestion of sedormid in a woman who had taken the drug several times a week over a period of two years. Sedormid the night before preceded two bouts of purpura and was induced in a trial administration. They report a similar picture in a woman following the use of phenobarbital, thrombocytopenia coming on four days after the development of a rather typical phenobarbital rash.

To these seven cases we add three cases observed by us as instances of thrombocytopenic purpura induced by sedormid.

REPORT OF CASES

CASE 1.—A woman, aged 37, seen Jan. 18, 1933, had marked purpura of the mucous membranes and skin, which had appeared on awakening that morning and had been present on two previous occasions two and three months before. Physical examination was negative except for the purpuric spots. The spleen was not palpable. There was no bleeding from the mucous membranes. There was no personal or familial history of allergy. The tourniquet test was markedly positive; hemoglobin was 96 per cent, red blood cells numbered 5,350,000 and white blood cells 5,200, with 63 per cent polymorphonuclear neutrophils, 30.5 per cent lymphocytes, 6 per cent mononuclear cells and 0.5 per cent eosinophilic polymorphonuclear leukocytes; the platelet count was 55,000 per cubic millimeter. Bleeding time was five minutes (Duke's method) and coagulation time thirty-two minutes (Howell's method). There was no clot retraction after forty-eight hours.

The patient advanced the information that she had taken one sedormid tablet the night before each of the three attacks and on about four or five occasions over a period of several months prior to the first attack. The purpuric manifestations disappeared within five to six days after observation, with a return to normal of the blood platelets and clot retraction. She refused any further trial with the drug and when last seen (1937) had had no recurrence of purpuric manifestations.



Hemorrhagic areas on buttocks in case 2.

CASE 2.—A white woman, aged 37, admitted to the Los Angeles General Hospital April 10, 1937, because of purpura, which had occurred the morning of admission, had had excellent health in the past except for a nervous breakdown at the age of 27. The morning of admission to the hospital she had awakened to find herself covered with purplish spots of varying size on nearly every part of the body. Her physician saw her at once and sent her to the hospital.

The purpuric spots were most numerous over both ankles and chiefly pea sized, but there were larger spots on the thighs, trunk and arms. Physical examination was negative except for these manifestations and some bleeding of the gums, with a 2 cm. hemorrhagic area on the pharyngeal wall. The blood pressure was 130 systolic, 96 diastolic. The spleen was not felt and there was no adenopathy present.

The patient had suffered no trauma. She had a normal menstrual history and was not menstruating on her admission to the hospital. She did not mention any drug therapy.

The Wassermann reaction was negative. The urine had a specific gravity of 1.020 and contained only a few red blood cells. Examination of the blood showed 4,760,000 red blood cells, hemoglobin 80 per cent and white blood cells 9,100, with 76 per cent polymorphonuclears and 24 per cent lymphocytes. The next day the hemoglobin was 90 per cent, red cells 4,570,000,

5. This committee is composed of Drs. George M. Coates, Lee Wallace Dean, Edmund Prince Fowler, Austin A. Hayden (chairman), Isaac H. Jones, Douglas MacFarlan, Burt R. Shurly, Horace Newhart and William P. Wherry. Mr. Howard A. Carter is secretary. Several of the individual members have availed themselves of the services of such physicists as Bunch, Fletcher, Hartig, Knudson and Rogers.

From the University of Southern California School of Medicine and the Los Angeles General Hospital.

1. Leschke, E.: Deutsche med. Wchnschr. **51**: 1352 (Aug. 14) 1925.
2. Pratt, J. H., in Osler's Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, **5**: 101, 1927.
3. Squier, T. L., and Madison, F. W.: Thrombocytopenic Purpura Due to Food Allergy, J. Allergy **8**: 143 (Jan.) 1937.
4. Maritschek, M., and Markowicz, H.: Hypersensitivity to Quinine with Purpura Haemorrhagica, Especially in the Upper Air and Food Passages, Monatschr. f. Ohrenh. **67**: 410 (April) 1933.
5. Peshkin, M. M., and Miller, J. A.: Quinine and Ergot Allergy and Thrombocytopenic Purpura, J. A. M. A. **102**: 1737 (May 26) 1934.
6. Loewy, F. E.: Thrombocytopenic Haemorrhagic Purpura Due to Idiosyncrasy Toward the Hypnotic Sedormid, Lancet **1**: 845 (April 21) 1934.
7. Dennig, H.: München. med. Wchnschr. **80**: 562 (April 14) 1933.
8. Purpura Haemorrhagica Following the Use of Allyl-Isopropyl-Acetyl-Carbamide, Vienna letter, J. A. M. A. **105**: 612 (Aug. 24) 1935.
9. Boas, E. P., and Erf, L. A.: Thrombocytopenic Purpura Following Medication with Sedormid and with Phenobarbital, New York State J. Med. **36**: 491 (April 1) 1936.

platelets 152,000, bleeding time five and one-half minutes, clotting time nine minutes and white blood cells 9,350 with 55.5 per cent polymorphonuclears, 32.5 per cent lymphocytes, 7 per cent monocytes, 0.4 per cent eosinophils and 1 per cent basophils. There was moderate toxic granulation with some shift to the left. The red blood cells appeared normal. Blood calcium was 9 mg. per hundred cubic centimeters of blood, total nonprotein nitrogen 20 mg. per hundred cubic centimeters. The patient had a temperature of 99.6 F. for several days and a mean pulse of 90. The stools were tarry and the benzidine test was strongly positive. The tourniquet test was markedly positive.

Blood Counts in Case 3

Date	Hemoglobin, per Cent	Erythrocytes	Leukocytes	Polymorphonuclears, per Cent	Lymphocytes, per Cent	Large Mononuclears and Transitionals, per Cent	Eosinophils, per Cent	Basophils, per Cent	Platelets
Sedormid 4 grains 5/4/37									
5/10/37	98	4,920,000	9,100	71	22	5	2	0	40,360
5/14/37	99	5,110,000	6,700	65	28.5	6	0.5	0	138,000
5/20/37	90	4,970,000	7,300	68	22.5	8.5	0.5	0.5	239,000
Sedormid 4 grains on retiring 5/20/37									
5/21/37	90	4,640,000	5,950	67.5	24	6.5	1.5	0.5	37,000
5/25/37	..	.....	.....	....	....	...	...	...	185,000
Reinstitution of bismarsen therapy									
6/ 2/37	90	4,810,000	6,950	65.5	24.5	7	2.5	0.5	428,000
6/ 4/37	..	4,850,000	.....	....	....	...	...	...	397,000

No abnormal cells were noted on any of the counts.

One week after admission, when the purpuric spots had practically faded and when she was generally improved, she was asked if she had ever taken sedormid. She replied that she had taken one-half tablet (2 grains, or 0.13 Gm.) the night before admission, but she didn't think it had anything to do with her illness. She further stated that she had taken an occasional tablet of the drug from time to time during the past three years. She felt that she had probably taken three full boxes of ten tablets each. She had not taken the drug for several weeks until the night before admission to the hospital.

In an endeavor to test the relation of the drug to her purpura she was given one tablet (4 grains, or 0.25 Gm.) on the night of April 20. A complete blood examination was ordered that day and unfortunately not performed. At 4 o'clock the next morning she was awakened by pain in the buttocks and she discovered two large purpuric spots there. By morning she had fresh showers of spots, larger on the average than those on admission, in the same general distribution. There was also a large painful spot on the right side of the tongue. The accompanying illustration shows the marked hemorrhagic areas on the buttocks. A platelet count done in the morning was 59,000. Three days later, with beginning fading of the purpura, the platelets numbered 91,000. A vitamin C estimation on a twenty-four hour urine showed an excretion of 66 mg. of vitamin C.

At this time the patient felt that she was being experimented on and left the hospital.

CASE 3.—A white man, aged 56, a traveling salesman, first seen in October 1935, was found by one of us (J. K.) to have a duodenal ulcer, clinically and radiologically distinctive, and tabes dorsalis with positive serologic reactions in both blood and spinal fluid. The blood count and urine were normal. In the past he had never had any purpuric tendency. His family history was negative. An appendectomy had been performed in 1917.

During 1935 and 1936 the patient had been given irregular antisyphilitic treatment and late in 1936 a series of intravenous typhoid injections for a severe arthritis. Since November 1935, from time to time, he had taken sedormid for sleeplessness.

During March and April 1937 the patient received intramuscular injections of 0.2 Gm. of bismarsen (bismuth arsphenamine sulfonate), the last dose on April 8. Four grains (0.25 Gm.) of sedormid was taken on retiring May 2 and May 4. During the night of May 8, purpura, manifested by bleeding from the gums and hemorrhagic vesicles on the tongue, buccal mucous membranes and skin, with scattered skin petechiae, became apparent. There was no fever and no other pertinent physical manifestation. The platelet count was 40,000.

On the night of May 20, the purpura having disappeared, the blood count being normal and the platelets up to 239,000, in order to determine which of his medicines, if any, had caused the purpura, another 4 grains of sedormid was given. Promptly during the night a repetition of the previous purpuric episode commenced, again with vesicular lesions, bleeding from the gums and skin petechiae, and again accompanied by a thrombocytopenia.

Reinstitution of bismarsen injections in doses of 0.2 Gm. intramuscularly May 25, June 4 and 11 was unattended by any sign of purpura or change in the blood picture.

COMMENT

The widespread use of sedormid without development of purpura at once raises the question of the character of the individual susceptibility to the drug. The problem is similar to the relationship of aminopyrine and dinitrophenol to the production of neutropenia. Here the benzamide radical seems to affect bone marrow with arrest of maturation of neutrophils. The carbamide radical of sedormid is under suspicion as the active agent in the production of thrombocytopenia, but the manner in which it acts is unknown. In all cases reported, including our three, the patient had taken the drug over many months without untoward effect. All likewise had had a short interval of freedom from ingestion of the drug before taking the one dose that immediately preceded the purpura. This suggests the development of an allergic sensitivity.

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THROMBOCYTOPENIC PURPURA FOLLOWING USE OF ALLYL-ISOPROPYL-ACETYL-CARBAMIDE (SEDORMID)

A. M. MOODY, M.D., SAN FRANCISCO

This brief report is made to record an unusual case of thrombocytopenic purpura which occurred following the taking of relatively small doses of a so-called harmless hypnotic, Sedormid-Roche (allyl-isopropyl-acetyl-carbamide).

A woman, aged 60, with mild diabetes, while vacationing during the summer of 1936 was advised by friends to take "Sedormid" tablets to obtain some restful sleep. Following this advice two tablets of 4 grains (0.26 Gm.) each were taken on one occasion. There were no ill effects noted. She had no occasion to take any more hypnotics until Feb. 6, 1937, when two 4 grain tablets were taken for sleeplessness. A similar dose was repeated February 9.

At 1 p. m. February 10 the patient noticed that her tongue felt quite thick; she looked at it in the mirror and noted several dark purple areas about one-fourth inch in diameter. The next morning (February 11) she saw many more on the tongue as well as large purple blotches on the skin. These areas were not painful. Brownish red blood was noted in the stool. She called her physician, who ordered her to go to the hospital.

The patient entered the St. Francis Hospital at 3 p. m. February 11, under the care of her personal physician, Dr. Harold Fraser, who has permitted me to report this case.

She walked into the hospital, was put to bed and laboratory examinations were made. At this time her temperature was 97 F., pulse 96, respiration rate 22. Her skin contained petechial and ecchymotic hemorrhages disseminated throughout, and there were many hemorrhages of the tongue and buccal mucosa. Examination of the blood revealed: red blood cells 3,760,000, hemoglobin 64.1 per cent (9.3 Gm.); leukocytes 10,700 with 72 per cent neutrophils, coagulation time four minutes, bleeding time thirty-five minutes; only an occasional platelet could be found. Thrombocytopenic purpura was diagnosed.

The patient was given 0.4 cc. of moccasin snake venom at 7 p. m. and then daily doses of 1 cc. each were given for the next few days. February 15 she received a transfusion of 500 cc. of whole blood. The bleeding time was down to eight minutes February 12 and down to three minutes February 14.

From the laboratory of the St. Francis Hospital.

On admission the urine contained only a few red cells, a trace of albumin, 0.5 per cent sugar and occasional hyaline casts.

The stools contained macroscopic blood until February 14. There were clots of blood in the stool passed at 1:30 a. m. on the 13th.

The patient continued to become weaker for the next few days, although no fresh hemorrhages were seen after twenty-four hours in the hospital. During the night of February 14 she was very restless and mentally confused. On the morning of February 15 the blood count was red blood cells 1,900,000, hemoglobin 32.7 per cent, coagulation time seven minutes, bleeding time 3 minutes and platelets 54,800. Following the transfusion given on this date the patient continued to improve and left the hospital March 1 in excellent condition.

In searching for a cause of the purpura the possibility of sedormid arose, and references to a few similar instances were found. Loewy[1] reported three cases. One of these patients submitted to several tests which proved conclusively a relationship between the drug and the thrombocytopenia. He states: "Severe loss of blood platelets and consequent hemorrhagic diathesis have been caused by the usual doses of Sedormid in certain hypersensitive patients who have received the drug for several months previously and with apparently good results." He suggests the possibility of an allergotoxic effect. Boas and Erf[2] reported in 1936 two cases of purpura, one each following medication with Sedormid and phenobarbital.

February 14, Dr. H. C. Davis consulted me with regard to causes of purpura and it was found that his patient had been taking Sedormid. The patient, a woman, aged 45, passing through the menopause, had taken Sedormid-Roche over a period of two weeks, from one to four tablets a day, in doses of one or two tablets at a time. During that period she had taken two boxes, a total of twenty tablets. When first seen, February 14, the patient had hemorrhages in the gums, both upper and lower, and on the right side of the mouth. February 15 the gums on both sides were hemorrhagic; there were two blood blisters near the tip of the tongue and a third starting on the right side of the tongue. There were two ecchymotic spots on the inner side of the lower lip. Around each wrist were isolated and confluent hemorrhagic areas with one or two on the dorsum of the second finger of the left hand. She had a nosebleed the same morning. At the end of five days all hemorrhages stopped. There was no blood in the urine or stools, according to the patient, who refused to have any examinations other than those which her physician could determine by inspection.

Blood Examinations

Date	Red Blood Cells per Cu.Mm.	Hemoglobin, per Cent	Hemoglobin, Gm. per Cent	White Blood Cells per Cu.Mm.	Polymorphonuclears, per Cent	Coagulation Time, Min.	Bleeding Time, Min.	Platelets
2/11/37	3,760,000	64.1	9.8	10,700	72	4	35	Rare
2/12/37	.....	....	....	7,600	70	5	8	16,348
2/14/37	2,140,000	40.9	5.98	10,200	59	8	3	45,570
2/15/37	1,920,000	32.7	5.5	7,500	59	7	3	54,857
2/16/37	2,900,000	55.7	8.0	8,100	55	6½	2½	23,200
2/17/37	3,270,000	58.9	8.5	10,500	70	5	2	96,470
2/19/37	3,090,000	60.5	8.78	10,400	59	4	2	154,500
2/20/37	3,260,000	62.8	9.0	10,700	46	4½	2	163,000
2/22/37	3,010,000	55.7	8.0	7,500	42	6	2	77,179
2/24/37	3,550,000	62.8	9.0	7,300	66	..	..	236,600
2/26/37	3,870,000	71.1	10.2	10,200	58	..	..	203,684
3/ 1/37	3,780,000	71.1	10.2	9,000	72	..	..	378,000

Wassermann and Kahn reactions negative

COMMENT

There are probably many more instances of these supposedly rare toxic reactions following the indiscriminate use of hypnotics, such as are herein reported, than the literature would lead one to believe. Physicians should accept a word of warning against these dangers.

The following statements from Cushny's Pharmacology[3] are important: "Much is still to be learned concerning the manifestations of idiosyncrasy and overdosage of the newer compounds, but there is no reason to believe that they differ markedly from those of barbital and phenobarbital. In fact most of the toxic signs and symptoms described in connection with earlier compounds have been experienced with those more recently introduced. . . . Not infrequently the hypnotics lead to skin eruptions, especially when used for some time. They assume various forms, the most common being of the erythema order, but among others urticaria, purpura, papular eruptions and blisters occur."

900 Hyde Street.

1. Loewy, F. E.: Lancet **1**: 845 (April 21) 1934.
2. Boas, E. P., and Erf, L. A.: New York State J. Med. **36**: 491 (April 1) 1936.
3. Edmunds and Gunn: Cushny's Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1936, pp. 367 and 365.

Special Article

THE CHEMISTRY OF THIAMIN (VITAMIN B_1)

ROBERT R. WILLIAMS, M.S., D.Sc.
NEW YORK

This article and others recently published or to be published comprise a new series on the present status of our knowledge of the vitamins. They have been prepared under the general auspices of the Council on Pharmacy and Chemistry and the Council on Foods. The opinions expressed are those of the authors and not necessarily the opinions of either council. The articles will be published later in book form.—ED.

A few years ago there appeared to be a hopeless conflict among the more or less empirical observations of the host of workers in the field of vitamin B. Fortunately the converging events since 1935 have established the chemical structure and certain properties of vitamin B_1 in a firm fashion. In order to emphasize that this factor is a definite chemical entity, distinct from all other substances, it may be well to use a distinctive name. For years the term antineuritic or antiberiberi vitamin had been used to designate this substance, but such names contain implications contrary to fact or beyond our knowledge; for example, that the relationship between neuritis and beriberi and this vitamin is mutually exclusive. In addition the name "vitamin" is subject to the objection that it brings under a common designation a group of substances which are chemically wholly unrelated to the best of our knowledge.

Prof. B. C. P. Jansen of Amsterdam, who, with W. F. Donath, first isolated the substance from natural sources in 1926,[1] suggested the name aneurin[2] for vitamin B_1. As a well deserved mark of respect for Professor Jansen, this name has come into extensive use in England and continental Europe. However, the name has been objected to on the ground of therapeutic implication and also because of its resemblance to the term aneurysm, which has long been used for a totally unrelated phenomenon. The latter objection seems to me more cogent. As to the former, a therapeutic implication, if based on genuine scientific information, has at least the merit of a memory aid. Many physicians must become confused by the arbitrary letters A, B, C and so on for the vitamins. In an endeavor to promote the adoption of a universally acceptable term, based on the chemistry of the substance, I have proposed "thiamin" (chloride, bromide, sulfate and so on) pending action of the Conference on Vitamin Standardization.

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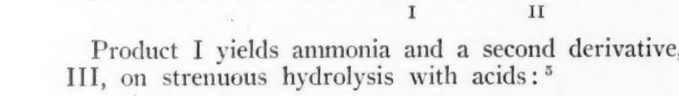
THE STRUCTURE OF THIAMIN

The greater part of the labor which has been expended on the chemistry of this substance had to do with its isolation. In addition to the difficulties due to its occurrence in the proportion of only 20 to 30 parts per million in the richest food sources, to its sensitivity to reagents and heat and to its nonselective solubilities, there were complications of confusion with physiologically similar substances, of shortcomings of bio-assays and of lack of the guidance of any general chemical theory. For these reasons the first isolation cost seventeen years of work in many lands, and adequate yields were not obtained until twenty-four years after the first serious attempts at chemical isolation were begun.

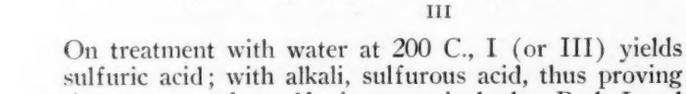
Once a few grams of the vitamin became available,[3] its structure was fully established in the relatively short space of three years and its synthesis followed almost immediately. As a participant throughout the several stages of the work I cannot in retrospect blame myself or my colleagues for the long delay. This was inherent in the nature of the problem.

Our knowledge of the structure of thiamin follows largely from the fact that it is quantitatively split by neutral sulfite solution at room temperature according to the equation [4]



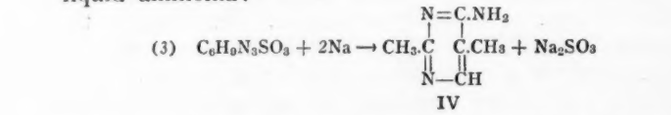
(1) $C_{12}H_{18}N_4SOCl_2 + Na_2SO_3 \rightarrow \underset{\text{I}}{C_6H_9N_3SO_3} + \underset{\text{II}}{C_6H_9NSO} + 2NaCl$

Product I yields ammonia and a second derivative, III, on strenuous hydrolysis with acids: [5]



(2) $C_6H_9N_3SO_3 + H_2O \rightarrow \underset{\text{III}}{C_6H_8N_2SO_4} + NH_3$

On treatment with water at 200 C., I (or III) yields sulfuric acid; with alkali, sulfurous acid, thus proving the presence of a sulfonic group in both. Both I and III exhibit absorption in the ultraviolet suggestive of a pyrimidine nucleus. This suggestion was later confirmed by converting I into 2, 5-dimethyl-6-aminopyrimidine, IV, by the action of metallic sodium in liquid ammonia: [6]

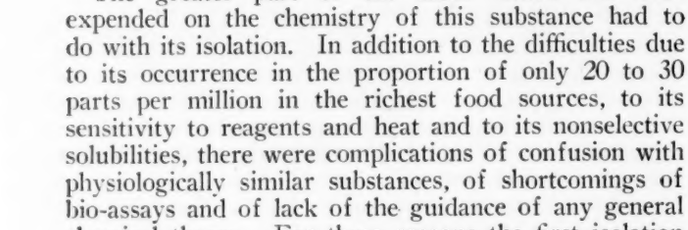


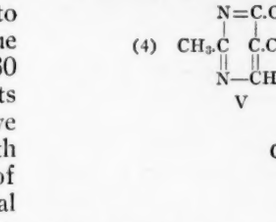
(3) $C_6H_9N_3SO_3 + 2Na \rightarrow$ $+ Na_2SO_3$

IV

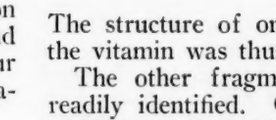
IV was previously unknown but its synthesis was effected by a method adapted from the literature [7] such as to establish its structure. Comparison with the substance obtained from the vitamin served to establish their identity.

By a similar synthesis we [8] obtained 2-methyl-5-ethoxymethyl-6-oxypyrimidine, V, which on treatment with sodium sulfite yielded 2-methyl-6-oxypyrimidine-5-methyl sulfonic acid, VI (equation 4), which proved identical [6] with III (equation 2), whence one could reconstruct the primary cleavage product, I (equation 1), as having structure VII.



(4) → 

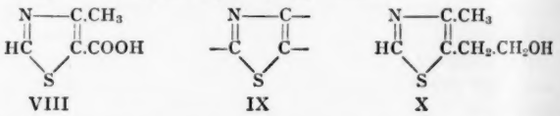
V VI



VII

The structure of one of the two main fragments of the vitamin was thus established.

The other fragment, II (equation 1), was more readily identified. On oxidation with nitric acid [9] it yielded 4-methyl-thiazole-5-carboxy acid, VIII, a substance which was first prepared synthetically in 1890.[10] The same substance had also been obtained by Windaus, Tschesche and Grewe [11] by oxidizing thiamin itself with nitric acid. Windaus, however, failed to recognize the thiazole nucleus, IX, which it contained. Recognition of this nucleus [12] by the peculiar stability of its sulfur atom was due to Dr. H. T. Clarke, who kindly collaborated with me at this stage of the study. The thiazole nucleus had never before been found in nature and its occurrence in thiamin is to be regarded as highly significant in a biochemical sense. With knowledge of the presence of this nucleus and with the further information that II (equation 1) contained in a side chain an alcoholic hydroxyl which could be readily replaced by nonionic chlorine [9] without alteration of the nucleus, it was a relatively simple matter to reconstruct the remaining vitamin fragment, II (equation 1), as having the structure X. It is called 4-methyl-5-(β-hydroxy) ethyl thiazole.



VIII IX X

In the identification of the cleavage products of thiamin, use was made to an unusual extent of comparisons of ultraviolet absorptions. This was possible because such a large proportion of all the atoms of the thiamin molecule are comprised in the two unsaturated nuclei; viz., pyrimidine and thiazole. Such nuclei have somewhat distinctive absorptions in the ultraviolet. Another physical method, that of potentiometric titration with alkali, was destined to disclose the mode of linkage of the two nuclei to each other.

The point of attachment on the pyrimidine portion was marked by the position of the sulfonic group which was introduced during the sulfite cleavage of thiamin. The point of attachment on the thiazole was less conspicuously marked. It was identified in the following way: Thiamin chloride on being titrated with alkali behaved in a peculiar manner.[13] After the addition of 1 mole of alkali, the alkalinity of the solution no longer rose steadily with further additions. Rather the alkalinity rose only temporarily after each addition and then fell again during the course of a few minutes, indicating an internal rearrangement of the molecule

3. Williams, R. R.; Waterman, R. E., and Keresztesy, J. C.: Larger Yields of Crystalline Antineuritic Vitamin, J. Am. Chem. Soc. **56:** 1187 (May) 1934.

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5. Williams, R. R.; Buchman, E. R., and Ruehle, A. E.: Studies of Crystalline Vitamin B_1: VIII. Sulfite Cleavage. II. Chemistry of the Acidic Product, J. Am. Chem. Soc. **57:** 1093 (June) 1935.

6. Williams, R. R.: Structure of Vitamin B_1, J. Am. Chem. Soc. **58:** 1063 (June) 1936. Cline, J. K.; Williams, R. R.; Ruehle, A. E., and Waterman, R. E.: Studies of Crystalline Vitamin B_1: XVI. Identification of the Pyrimidine Portion, ibid. **59:** 530 (March) 1937.

7. Williams, R. R.; Ruehle, A. E., and Finkelstein, Jacob: Studies of Crystalline Vitamin B_1: XV. C-Methylated 6-Amino- and 6-Oxypyrimidines, J. Am. Chem. Soc. **59:** 526 (March) 1937.

8. Cline, J. K.; Williams, R. R., and Finkelstein, Jacob: Studies of Crystalline Vitamin B_1: XVII. Synthesis of Vitamin B_1, J. Am. Chem. Soc. **59:** 1052 (June) 1937.

9. Buchman, E. R.; Williams, R. R., and Keresztesy, J. C.: Studies of Crystalline Vitamin B_1: X. Sulfite Cleavage. III. Chemistry of the Basic Product, J. Am. Chem. Soc. **57:** 1849 (Oct.) 1935.

10. Wöhmann, M.: Ann. d. Chem. **259:** 299, 1890.

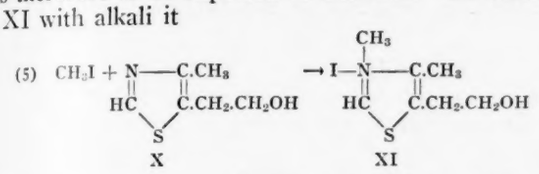
11. Windaus, A.; Tschesche, R., and Grewe, R.: Ueber das antineuritische Vitamin, Ztschr. f. physiol. Chem. **228:** 27 (Oct. 3) 1934.

12. Clarke, H. T., and Gurin, S.: Studies of Crystalline Vitamin B_1: XII. The Sulfur-Containing Moiety, J. Am. Chem. Soc. **57:** 1876 (Oct.) 1935.

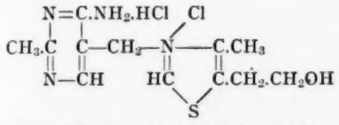
13. Williams, R. R., and Ruehle, A. E.: Studies of Crystalline Vitamin B_1: XI. Presence of Quaternary Nitrogen, J. Am. Chem. Soc. **57:** 1856 (Oct.) 1935.

taking place not instantly as ionic reactions do but relatively slowly. Furthermore, this deportment continued until a total of 3 moles of alkali had been added. Only then was there a marked and steady rise in alkalinity. The excessive proportion of alkali required was wholly unexpected at the time, as thiamin was known to contain only 2 acid radicals.

It was found possible to add methyl iodide to X to form XI.[9] Such an addition of methyl iodide is a very general property of tertiary nitrogenous bases and was therefore to be expected in this case. On titration of XI with alkali it

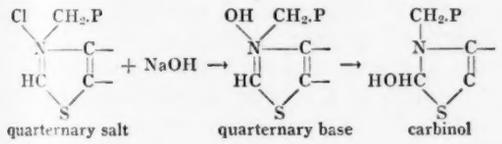


showed the same peculiar behavior as thiamin, thus pointing to a fundamental kinship which could be accounted for only by assigning to thiamin the following structure, XII:[6]

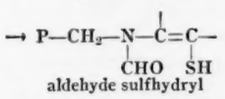


XII. Thiamin chloride hydrochloride

The peculiar behavior of these quaternary thiazole salts with alkali is due not to a single rearrangement but to two successive rearrangements of the thiazole portion of the molecule:[14]



quarternary salt — quarternary base — carbinol

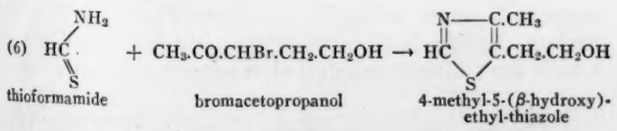


aldehyde sulfhydryl

in which P represents in the case of thiamin the pyrimidine nucleus and its substituent groups. The final mole of alkali is required to neutralize the acidic —SH group which is formed when the thiazole ring opens. On addition of acid the series of steps is reversed and the quaternary thiazole, e. g., thiamin, is recovered unchanged. This behavior as well as the sulfite cleavage is an outstanding peculiarity of the unique thiamin molecule. Nature evidently has chosen some aristocratic molecules for the performance of certain of her distinctive biochemical tasks.

SYNTHESIS OF THIAMIN

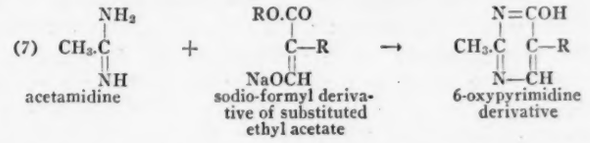
The first step in the synthesis of thiamin was the reproduction of the thiazole portion. This was first done by my associate Dr. E. R. Buchman[15] by the simple reaction:



thioformamide — bromacetopropanol — 4-methyl-5-(β-hydroxy)-ethyl-thiazole

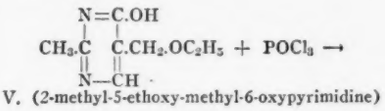
Other syntheses of the same compound also have been achieved.[12]

The synthesis of the pyrimidine portion was accomplished by methods similar to those employed for the production of pyrimidines IV, V and VI, previously discussed in connection with the establishment of structure. The general method is as follows:[16]

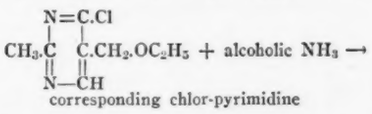


acetamidine — sodio-formyl derivative of substituted ethyl acetate — 6-oxypyrimidine derivative

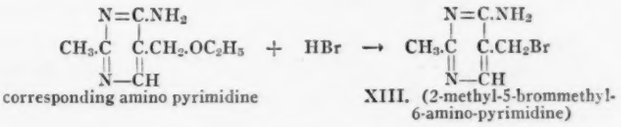
If in the foregoing sodioformyl derivative R represents CH_3, the pyrimidine obtained is 2, 5 dimethyl-6-oxypyrimidine; if R represents $CH_2OC_2H_5$ the resulting pyrimidine is V (equation 4). For the synthesis of thiamin itself, product V is converted into a brom amino derivative, thus:



V. (2-methyl-5-ethoxy-methyl-6-oxypyrimidine)



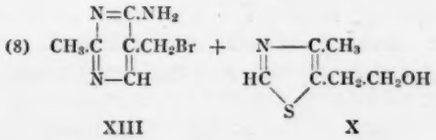
corresponding chlor-pyrimidine



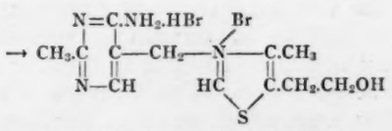
corresponding amino pyrimidine — XIII. (2-methyl-5-brommethyl-6-amino-pyrimidine)

The last of this series of steps is somewhat analogous to that of equation 4. The purpose of putting the Br in the side chain in position 5 instead of the sulfonic group is that the brom compound XIII is very reactive, while the corresponding sulfonic compound VII is extremely unreactive. My associate Dr. J. K. Cline was in large measure responsible for the success of these pyrimidine syntheses and the final condensation.

The final step in the synthesis of thiamin is to heat the hydrobromide of the brompyrimidine, XIII, with the thiazole, X. This results in combination of the two molecules to form thiamin bromide hydrobromide quite analogous to the reaction shown in equation 5.



XIII — X



XIV. Thiamin bromide hydrobromide

The bromide hydrobromide, XIV, is readily converted into the chloride hydrochloride, XII, simply by shaking a solution of the former with silver chloride. The resulting substance is chemically identical[17] with the thiamin chloride previously obtained from nature. The correspondence of the ultraviolet absorption spectrums of the two synthetic salts with that from nature

14. Mills, W. H.; Clark, L. M., and Aeschlimann, J. A.: J. Chem. Soc. **123**: 2353, 1923.

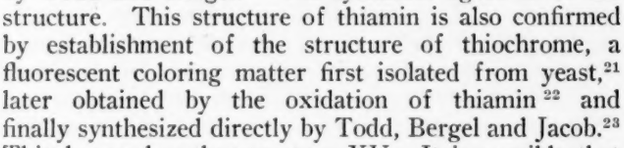
15. Buchman, E. R.: Studies of Crystalline Vitamin B_1: XIV. Sulfite Cleavage. IV. The Thiazole Half, J. Am. Chem. Soc. **58** 1803 (Sept.) 1936.

16. Williams, R. R., and Cline, J. K.: Synthesis of Vitamin B_1, J. Am. Chem. Soc. **58**: 1504 (Aug.) 1936. Cline, Williams and Finkelstein.[8]

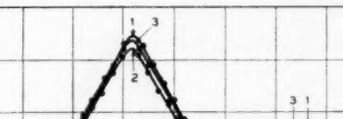
17. Williams, R. R., and Cline, J. K.: Synthetic Vitamin B_1, J. Am. Chem. Soc. **59**: 216 (Jan.) 1937.

is shown in the accompanying chart. Its physiologic action is also identical.[18]

Another synthesis of thiamin by Andersag and Westphal has been announced by Grewe [19] but has not been fully described. Still another synthesis is given by Todd and Bergel.[20] All syntheses agree as to the structure. This structure of thiamin is also confirmed by establishment of the structure of thiochrome, a fluorescent coloring matter first isolated from yeast,[21] later obtained by the oxidation of thiamin [22] and finally synthesized directly by Todd, Bergel and Jacob.[23] Thiochrome has the structure XV. It is possible that thiochrome plays a role as an intermediate in the functioning of thiamin in tissues. I tentatively prefer the view that thiochrome is merely a natural degradation product of thiamin which has already passed the useful stage. It is inactive.



A comparison of the ultraviolet absorptions of the natural and synthetic products: curve 1, natural vitamin (hydrochloride); curve 2, synthetic vitamin (hydrochloride); curve 3, synthetic vitamin (hydrobromide).



XV. Thiochrome

BIOCHEMISTRY OF THIAMIN

The reactions of thiamin are important particularly for three reasons: (1) They may result in loss of the natural supply by improper methods of distributing and preparing foods; (2) they may serve as a basis for the devising of adequate chemical methods of assaying foods, concentrates and body secretions; (3) they are of interest for the interpretation of the mode of functioning of the substance in living tissues.

Under the first head the most important consideration is the lability of thiamin in neutral mediums. This lability is well exemplified by the ease of cleavage by sulfite at p_H 5 to 6. This cleavage is not peculiar to solutions containing sulfite. Barium nitrite or sodium acetate effects splitting in a similar sense and it seems probable that in neutral foods free thiamin is very subject to corresponding splitting under influences which are as yet imperfectly understood. At high acidity this type of cleavage of thiamin does not occur. Probably other constituents of tissues and fluids often participate in destructive reactions when the medium is neutral. Since thiamin is never present in more than a few parts per million, other constituents are in general present in overwhelming proportions.

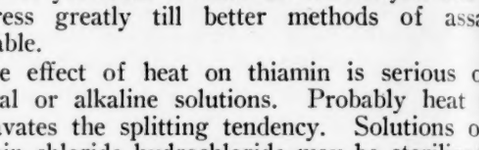
In spite of this fact, loss of B_1 activity in cooking of foods is sometimes negligibly small. Quite possibly the stability of thiamin in foods is to a great extent due to its existence in combined form, e. g., the pyrophosphoric ester, which will be discussed later. Loss by leaching during cooking is probably more serious than by heat destruction, though the latter is also substantial if cooking is prolonged for hours or is carried out at temperatures above 100 C., especially if the reaction of the foodstuff is not markedly acid. We have yet much to learn on this subject but cannot progress greatly till better methods of assay are available.

The effect of heat on thiamin is serious only in neutral or alkaline solutions. Probably heat merely aggravates the splitting tendency. Solutions of pure thiamin chloride hydrochloride may be sterilized without loss by heating to 120 C. for a half hour or more.[24] This stability is due to the acidity of this salt, which gives solutions of approximately p_H 3.5.

The oxidation of thiamin to thiochrome has already been mentioned. The importance or extent of this reaction in the foods or in the body is quite unknown. Reduction of thiamin has also been studied by Lipmann [25] and is rather suggestive of a possible mode of functioning of thiamin in living things. Reduction of thiamin with platinum black results in the addition of two hydrogen atoms; reduction with hydrosulfite adds one hydrogen and produces a mole of acid. A similar contrast in the behavior of these two reducing agents is found in their action on a dehydrogenating coferment isolated from red blood cells by Warburg and his co-workers.[26] This suggests a possible dehydrogenase function of thiamin.

BIOCHEMICAL LESION IN THIAMIN DEFICIENCY

A more tangible and better defined relationship of thiamin to an enzyme is found in the work of Löhmann and Schuster,[27] who isolated from yeast a crystalline derivative of thiamin having the structure:



It is the pyrophosphoric ester of thiamin. This substance is split also by sulfite to form the same products which thiamin yields, except that the thiazole is obtained in pyrophosphorylated form rather than free. The ester is antineuritic, though less so than thiamin. It also functions as a cocarboxylase with a protein or proteins present in washed yeast cells and in such an enzyme system strongly promotes the evolution of carbon dioxide from a pyruvate-phosphate medium in which the cells are suspended, a property which is lack-

18. Eckler, C. R., and Chen, K. K.: Action of Synthetic Vitamin B_1, Proc. Soc. Exper. Biol. & Med. **35**: 458 (May) 1937.
19. Grewe, Rudolf: Ueber das antineuritische Vitamin, Ztschr. f. physiol. Chem. **242**: 89 (Aug. 3) 1936.
20. Todd, A. R., and Bergel, F.: J. Chem. Soc., March 1937, p. 364.
21. Kuhn, R.; Rudy, H., and Wagner-Jauregg, T.: Ber. Deutsche. chem. Gesellsch. **66**: 1950, 1933.
22. Barger, G.; Bargel, F., and Todd, A. R.: Nature **136**: 259, 1935; Ber. Deutsche chem. Gesellsch. **68**: 2257, 1935. Kuhn, R., and Vetter, H. Ber. Deutsche chem. Gesellsch. **68**: 2384, 1935.
23. Todd, A. R.; Bergel, F., and Jacob, A.: J. Chem. Soc., 1936, p. 1555.
24. Molitor, H., and Sampson, W. L.: E. Merck, Jahresbericht, 1936.
25. Lipmann, Fritz: Hydrogenation of Vitamin B_1, Nature **138**: 1097 (Dec. 26) 1936.
26. Warburg, Otto; Christian, Walter, and Griese, Alfred: Wasserstoffübertragendes Co-Ferment, seine Zusammensetzung und Wirkungsweise, Biochem. Ztschr. **282**:157 (Nov. 21) 1935. Karrer, Paul, and Warburg, Otto: Jodmethylat des Nicotinsäureamids, ibid. **285**: 297 (May 12) 1936.
27. Löhmann, K., and Schuster, P.: Naturwissenschaften **25**:26 (Jan. 8) 1937. Löhmann, K.: Ztschr. f. angew. Chem. **50**:233 (March) 1937.

ing in free thiamin. The cocarboxylase is thought to promote the reaction:

$$\underset{\text{pyruvic acid}}{CH_3.CO.COOH} \rightarrow \underset{\text{acetaldehyde}}{CH_3.CHO} + CO_2$$

The cocarboxylase is oxidized with alkaline ferricyanide to a thiochrome-like substance. One phosphoric acid group is readily hydrolysed off, the second with difficulty.

The cocarboxylase also has the property of promoting oxygen uptake in vitro of slices of polyneuritic brain tissue in a pyruvate medium, a property previously shown by Peters to be characteristic of pure thiamin. The work of Peters and his associates on this subject is contained in a large number of papers, but since the ideas of the authors have undergone a number of changes the reader will do well to refer first to the latest papers.[28] Those in *Current Science* and the *Lancet* are summaries. The principal finding is that as polyneuritis develops in pigeons the brain tissue loses its power to respire and pyruvic acid accumulates in it. Administration of thiamin corrects these faults in the animal. It also destroys pyruvic acid and promotes respiration of the tissue in vitro. Pyruvic acid is regarded as a normal intermediary in carbohydrate metabolism, which is not properly disposed of in the polyneuritic state. This abnormality is not wholly confined to the brain tissue but is present to some extent in the kidney and heart muscle.

Recently a paper by Westenbrink and Pollak[29] has brought Peters' older observations into even close relationship with the later ones of Löhmann and Schuster. This paper confirms the tissue respiration work of Peters and his associates and adds the interesting observation that there is a ten minute induction period before oxygen uptake begins after the addition of thiamin to a medium containing polyneuritic brain tissue. Westenbrink and Pollak postulate the necessity of thiamin combining with something else before it begins to function. Had they seen Löhmann and Schuster's work before publishing their results they doubtless would have been tempted to assume pyrophosphorylation as the necessary intermediate step.

All these results relating thiamin to the disposal of accumulated pyruvic acid in polyneuritic tissues is of tremendous interest in view of the finding by Platt and Lu[30] of considerable quantities of pyruvic acid in the blood of patients with beriberi. Indeed, it seems almost certain that the disposal of pyruvic acid by an enzymic decarboxylation is one of the functions of thiamin. Thiamin in pyrophosphorylated form may well constitute the prosthetic group of this enzyme just as riboflavin, B_2, in phosphorylated form constitutes the prosthetic group of a dehydrogenating enzyme.[31]

However, many points remain to be cleared up before it can be said that this is the sole or even principal function of thiamin. Particularly it is not yet clear precisely how promotion of oxygen uptake is related to decarboxylation. In addition there is an extensive literature which attempts to associate methyl glyoxal (pyruvic aldehyde) rather than pyruvic acid with the beriberic condition. Peters found no methyl glyoxal in polyneuritic brain tissue of pigeons,[32] but it has been reported by others in the urine of B_1 deficient infants,[33] of B_1 deficient rats[34] and in liver extracts of B_1 deficient animals.[35] Moreover, there is an extended series of voluminous articles of Japanese origin chiefly in the Tohoku *Journal of Experimental Medicine* during the past fifteen years which greatly emphasizes the occurrence in the milk of mothers with beriberi of a methyl glyoxal-like substance and also a deficiency of a normal peroxidase in the milk and blood leukocytes. The Japanese authors emphasize the toxic character of this milk. Mice on a polished rice diet die in from one to five days if injected daily with milk from mothers with beriberi or rabbits with polyneuritis, while normal milk has no effect.[36] In women, one breast may secrete toxic milk, the other nontoxic.[37] There are from seventy-five to eighty papers along these lines in this one journal during the past fifteen years. They deserve careful study but have been generally neglected. One of the most impressive papers is by Chiba,[38] as it gives detailed data on many scores of human beriberi cases.

The function of thiamin is probably not merely to get rid of pyruvic acid but to utilize it in some metabolic process. Thiamin has been shown to play a fundamental role in the physiologic economy of plants. It promotes alcoholic fermentation by yeast;[39] it is essential to growth of excised embryos of seeds influencing root production profoundly.[40] According to the results of W. J. Robbins, Mary H. Bartley, A. G. Hogan and others,[41] plants and, to some extent, animals have a capacity for synthesizing thiamin if supplied with the intermediates used in its artificial synthesis. Thiamin functions in the economy of a wide variety of micro-organisms, in the lower and higher plants, and in insects as well as in all higher animals. One can scarcely regard it otherwise than as one of nature's earlier and more fundamental inventions in the process of evolving life. It is difficult to believe that its action in the higher forms of life is restricted to specialized tissues or to a narrow function.

METHODS OF ASSAY AND DISTRIBUTION IN FOODS

The existing methods of assay are wholly biologic in nature and are not entirely satisfactory. The method most widely used for testing foods is the rat growth method. It gives fairly consistent results but cannot be highly specific as it involves the unwarranted assumption that there are no thermolabile vitamins in yeast or in foods generally other than thiamin. The rat curative method[42] is more specific but it has not been developed or even tried extensively for food testing purposes. Also the international standard of

28. Peters, R. A.: Pyruvic Acid Oxidation in Brain: I. Vitamin B_1 and the Pyruvate Oxidase in Pigeon's Brain, Biochem. J. **30**: 2206 (Dec.) 1936; Lancet **1**: 1161 (May 23) 1936; Current Science **5**: 207, 1936.

29. Westenbrink, H. G. K., and Pollak, J. J.: Rec. trav. chim. Pays. Bas. **56**: 315, 1937.

30. Platt, B. S., and Lu, G. D.: Chemical and Clinical Findings in Beriberi, with Special Reference to Vitamin B_1 Deficiency, Quart. J. Med. **5**: 355 (July) 1936.

31. Tauber, Henry: Enzyme Chemistry, New York, John Wiley & Sons, Inc., 1937.

32. Peters, R. A.: Current Science **5**: 207, 1936.

33. Geiger, A., and Rosenberg, A.: Methylglyoxal im Harne und in der Cerebrospinalflüssigkeit bei Ernährungsstorungen der Säuglinge mit toxischen Symptomen und bei der experimentellen B_1-Avitaminose bei Hunden und Ratten, Klin. Wchnschr. **12**: 1258 (Aug. 12) 1933.

34. Lehmann, Jörgen: Ist das Vorkkommen von Methylglyoxal im Harn Spezifisch für B_1-Avitaminose? Skandinav. Arch. f. Physiol. **71**: 157 (Feb.) 1935.

35. Vogt-Møller, J.: Ist Avitaminosis B_1, eine Intoxikation mit Methylglyoxal? Biochem. Ztschr. **233**: 248 (April 22) 1931.

36. Asakura, Kyumatsu, and Ohsako, Hujio: Arakawa's Reaction and Toxicity of Human Milk, Tohoku J. Exper. Med. **20**: 429 (March) 1933.

37. Asakura, Kyumatsu: Relation Between Arakawa's Reaction and Suitability of Human Milk, Tohoku J. Exper. Med. **19**: 275 (Aug.) 1932.

38. Chiba, Marié: Prolongation of Short-Timed Peroxidase Reaction of Leukocytes as a Sign of Avitaminosis B and Effect of Vitamin B on It: A Clinical Experiment, Tohoku J. Exper. Med. **19**: 486 (Sept.) 1932.

39. Schultz, Alfred; Atkin, Lawrence, and Frey, C. N.: A Fermentation Test for Vitamin B_1, J. Am. Chem. Soc. **59**: 948 (May) 1937.

40. Kögl, Fritz, and Haagen-Smit, A. J.: Biotin und Aneurin als Phytohormone, Ztschr. f. physiol. Chem. **243**: 209 (Oct. 14) 1936. Bonner, James: Vitamin B_1 a Growth Factor for Higher Plants, Science **85**: 183 (Feb. 12) 1937. Robbins, W. J., and Bartley, M. H.: Vitamin B_1 and the Growth of Excised Tomato Roots, Science **85**: 246 (March 5) 1937.

41. Robbins, W. J.; Bartley, Mary A.; Hogan, A. G., and Richardson, L. R.: Pyrimidine and Thiazole Intermediates as Substitutes for Vitamin B_1, Proc. Nat. Acad. Sc. **23**: 388 (July) 1937.

42. Smith, M. I.: Pub. Health Rep. **45**: 116 (Jan. 17) 1930.

reference is an acid clay adsorbate which, because of the firm combination of thiamin with the clay, may not yield its thiamin fully in animal assays,[43] the availability varying according to the condition of the animals. This has led to endless confusion.

It will be no easy matter to devise a satisfactory method of chemical assay for thiamin in foods. It occurs in the proportions of only from 0.1 to 4 parts per million, roughly a thousand times less abundant than vitamin C. It possesses no known physical property which is adapted to delicate testing. Jansen[44] has proposed to convert it to thiochrome, which can be estimated optically; but a quantitative conversion has not yet been achieved. A more promising lead is that of McCollum and Prebluda,[45] who couple it with diazotized para-amino-acetophenone to form a red dye which may be estimated colorimetrically. An efficient method of extracting the vitamin from foods will be necessary for the application of such assay methods.

DIAGNOSTIC TESTS

It has been proposed to assay the urine as a diagnostic test of thiamin deficiency in patients, and some evidence of success has been cited.[46] My experience with this method has been limited to a single individual with severe diabetes. In this instance the patient was receiving 40 mg. of thiamin daily, of which no more than 1 mg. appeared in the urine in a day. The tests were repeated three times at intervals of several days while the daily dosage was continuously maintained. In view of this experience two years ago, I believe that many data will be necessary to establish suitable norms for diagnostic purposes, even though it is found that there is prevailingly a fixed ratio between ingested thiamin and that excreted in the urine. It may well be that there is a variable destruction in the body or elimination in the feces.

The therapeutic response to thiamin remains the most trustworthy diagnostic test which we have. It is quite safe, as doses of as high as 90 mg. have evidenced no pharmacologic effect in human subjects.[47] Rats have received as high as 5 mg. daily throughout life for three successive generations without adverse effects. This corresponds on a weight basis to about 1 Gm. daily for the human adult. Doses of from 2 to 10 mg. daily for several weeks are therefore extremely conservative for human treatment. The daily intake in food for human adults is of the order of 1 to 2 mg.; the requirement is proportional to the food intake and particularly to the carbohydrate intake.

The diagnostic value of thiamin therapy is largely lost if crude natural preparations are used both because of the uncertainty of their standardization and of the presence of other vitamins which may be responsible for the observed effects. After demonstrating a B_1 deficiency and rectifying the immediate shortage, the physician should endeavor to direct the diet of the patient toward a more adequate supply of the vitamin. In the long run we should look to the grocery store rather than the drug store for a normal intake.

43. Sampson, W. L., and Keresztesy, J. C.: Proc. Soc. Exper. Biol. & Med. **36**: 30 (Feb.) 1937.
44. Jansen, B. C. P.: Rec. trav. chim. Pays. Bas. **55**: 1046, 1936.
45. Prebluda, H. P., and McCollum, E. V.: A Chemical Reagent for the Detection and Estimation of Vitamin B_1, Science **84**: 488 (Nov. 27) 1936.
46. Harris, L. J., and Leong, P. C.: Vitamins in Human Nutrition, The Excretion of Vitamin B_1 in Human Urine and Its Dependence on the Dietary Intake, Lancet **1**: 886 (April 18) 1936. Helmer, O. M.: Vitamin B_1 and B_2 Content of Human Urine, Proc. Soc. Exper. Biol. & Med. **32**: 1187 (April) 1935. Roscoe, Margaret H.: The B Vitamins in Human Urine, Biochem. J. **30**: 1053 (June) 1936.
47. Vorhaus, M. G.; Williams, R. R., and Waterman, R. E.: Studies on Crystalline Vitamin B_1: Observations in Diabetes, Am. J. Digest. Dis. & Nutrition **2**: 541 (Nov.) 1935.

Therapeutics

THE THERAPY OF THE COOK COUNTY HOSPITAL

EDITED BY BERNARD FANTUS, M.D.
CHICAGO

NOTE.—*In their elaboration, these articles are submitted to the members of the attending staff of the Cook County Hospital by the director of therapeutics, Dr. Bernard Fantus. The views expressed by various members are incorporated in the final draft for publication. The articles will be continued from time to time in these columns. When completed, the series will be published in book form.*—ED.

THE THERAPY OF ICTERUS (JAUNDICE)

IN COLLABORATION WITH DR. FREDERICK STEIGMANN

Icterus is merely a symptom, the clinical significance of which must be determined before treatment can be addressed to it. On the differential basis of bilirubinuria one may distinguish between true icterus (or "manifest jaundice") and false icterus.

True icterus is a positive balance in retained bile pigment (bilirubin) of sufficient intensity to stain the plasma, the sclera, the urine and finally the skin and the mucous membranes. From a therapeutic standpoint it must be differentiated from (A) pseudo-icterus and

Differential Characteristics of Varieties of Icterus

Variety	Icterus Index	Stercobilin	Urobilinuria	Bilirubinuria	Choluria
A. Pseudo-icterus.....	4-6 Negative van den Bergh	+	0	0	0
B. Subicterus.....	6-15	+	+0	0	0
C. Hyperhemolysis icterus	More than 15	+	+	+	0
D. Obstructive icterus.....	More than 15	0	0	+	+
E. Hepatosis icterus.....	More than 15	+	+	+	+0

(B) subicterus. When true jaundice is present, one must distinguish between (C) hyperhemolysis icterus, (D) obstructive icterus and (E) hepatosis [1] icterus. To this must be added (F) icterus of the new-born, which may assume any one of these types.

It must be recognized that there are all possible conditions intermediate between these clinical types. Subicterus may develop into true icterus. Hyperhemolysis jaundice may become obstructive from extreme viscosity of bile. Obstruction may be partial, so that some bile enters the bowel. The obstruction may be intermittent. Hepatosis jaundice may follow any of the other forms, and acholic stools may develop in the course of hepatosis icterus. Nevertheless, the distinctions are valid from the therapeutic standpoint, since the treatment is governed chiefly by the type of jaundice present.

A. PSEUDO-ICTERUS (FALSE JAUNDICE)

Carotenemia due to the eating of large quantities of carrots (e. g., in diabetes) is characterized by lack of staining of the sclera, by a negative van den Bergh reaction (test 7), and by the disappearance of the serum discoloration and later of that of the skin on withdrawal of carrots from the diet.

Painting of the skin with picric acid in malingering is distinguished by the icterus index being normal (from 4 to 6) and the sclera free from bile pigment. When

1. The term "hepatosis" is employed here with the meaning of "extensive degeneration of liver parenchyma cells."

the condition is due to absorption from the application of picric acid to burns or from ingestion, the sclerae are also stained but the urine is free from bile and it contains picramic acid.

B. SUBICTERUS

Diagnosis.—Subicterus, which might also be called latent jaundice or acholuric jaundice, is characterized by yellow discoloration of the skin, by urobilinuria (test 2) and by moderately increased (below 15) icterus index (test 6) but by the absence of bilirubinuria (test 3), since it requires 1 : 50,000 bilirubin content of the plasma (4 units van den Bergh) before bile appears in the urine. There is no choluria (test 4) and the stools are of normal color.

Treatment.—While subicterus is merely an incidence of no direct therapeutic significance in most conditions —such as pneumonia or malaria, septicemia, pernicious anemia, hepatic cirrhosis or hepatic syphilis—its detection is important (*a*) in patients exposed to poisons, industrial or medicinal, e. g., those undergoing arsphenamine treatment, and (*b*) in chronic hemolytic jaundice.

(*a*) Toxic Subicterus: This may occur during arsphenamine therapy or when cinchophen is given, or in persons who are industrially exposed to nitrophenol or to aromatic nitroderivatives of benzene, such as dinitrobenzene and phenylhydrazine.

Such individuals should be watched for yellow discoloration of the skin and have routine examinations of the blood icterus index, as this is the best means of detecting the condition early.

The appearance of subicterus calls for (1) immediate cessation of the injections of arsphenamine or the removal of the patient from exposure to the industrial poison; (2) the free administration of carbohydrate (sugar by mouth, dextrose intravenously) to protect the liver cells; (3) giving an abundance of water and (4) calcium administration, which may also be of value. When the arsenicals have been given the administration of sodium thiosulfate, 1 Gm. by mouth three times a day and by vein 1 Gm. in 20 cc. of water daily until the jaundice disappears, is indicated. In hepatic syphilis the arsenicals are contraindicated.

(*b*) Chronic Hemolytic Jaundice: This is of therapeutic importance because splenectomy is curative in this condition. It is a disease of the blood-forming organs characterized by abnormal shape and fragility of the erythrocytes (test 10) (hemolysis between 0.6 and 0.42 per cent of sodium chloride), microcytic anemia and large numbers of reticulated cells, splenomegaly, urobilinuria but not bilirubinuria, normally colored feces and no cholemia. It is generally a congenital or familial disease but may be acquired. Patients are subject to exacerbations following chilling, exertion or excitement. Febrile attacks with biliary colic due to pigment calculi may occur. Splenectomy should be performed during a period of quiescence of the disease and be preceded by a blood transfusion.

C. HYPERHEMOLYSIS ICTERUS

Hyperhemolysis icterus is due to hemolysis sufficient in degree to produce bilirubinuria.

Diagnosis.—This form of jaundice is characterized by bilirubinuria (test 3) without choluria (test 4). Since in this condition there is no anomaly of excretion of bile salts, the bile acids are absent from the urine (dissociated icterus). Even though the icterus may become very deep, the itching, bradycardia and tendency to bleeding are absent, since the bile pigments themselves are devoid of toxicity. It is only when "cholemia" or the retention of all the other bile products in the blood exists that these toxic effects manifest themselves.

Hyperhemolysis jaundice accompanies conditions in which there is increased hemoclasis (leukemia, chronic nitrophenol, or nitrobenzene or phenylhydrazine poisoning) and in those conditions in which hemoglobin is destroyed by phagocytosis and hemosiderosis results (pernicious anemia, malaria, blackwater fever, long continued septicemia). In myeloid leukemia the destruction of hemoglobin is due to encroachment of myeloblastic on erythroblastic marrow, with destruction of the latter. The same condition operates in metastasis of neoplasms to the bone marrow; the myelophthitic anemia thus produced is, if rapid in its evolution, accompanied by jaundice.

Treatment.—The condition may be physiologic and not require any treatment, as in icterus neonatorum (q. v.), in which the lysis of the nucleated erythrocytes liberates hemoglobin, the bile pigments from which may be produced so rapidly as to clog the bile canaliculi, resulting in a partially obstructive jaundice.

In pernicious anemia the preformed hemoglobin never finds an adequate stroma to enclose it and may undergo decomposition along the same pathway as hemoglobin liberated by hemolysis from a previously intact corpuscle. The treatment of this condition is the giving of the specific stroma building substance present in the liver or stomach (cf. Pernicious Anemia). When an erythrogenic response is reached through the agency of such treatment, the jaundice from this source disappears.

The treatment of the other forms of this type of jaundice, as for example that accompanying the accelerated destruction of red blood cells in septicemia, will depend on an appreciation of the primary factors involved.

D. OBSTRUCTIVE ICTERUS

Recognition.—In obstructive icterus the skin and sclerae are stained, the icterus index (test 6) is high and there is bilirubinuria (test 3) but no urobilinuria (test 2) because there is no stercobilin in the stools (test 1). There is also choluria, i. e., elimination of bile salt in the urine (test 4) because there is an excess of these salts in the blood (cholemia) which results in bradycardia, itching, drowsiness, headache, delirium and coma. Hypercholesteremia (test 9) has the same diagnostic significance as choluria. A hemorrhagic tendency often supervenes.

As acholic stools may also occur in the later stages of hepatosis jaundice, the presence of which contraindicates surgical treatment, and since hepatic degeneration may develop in the course of obstructive jaundice, liver function tests are of practical importance. Of these the carbohydrate metabolism tests (tests 5 and 8) are the most easily performed, but extensive damage to the liver cells must be present before the changes are reflected by deranged carbohydrate metabolism. The dextrose tolerance test (test 8) is based on the observation that in obstructive jaundice the blood sugar curve continues upward at the end of two hours, while in hepatosis jaundice the curve has returned to or below the initial level by this time. The galactose tolerance test (test 5), which is a simpler test since it merely requires urinalysis, yields an output of less than 3 Gm. in obstructive jaundice. In the present state of ignorance as to the relative importance of liver function tests, several others may have to be resorted to in a difficult case, most especially since there may be a dis-

sociation of the liver function; i. e., one function may be much more injured than another. (See Additional Liver Function Tests Worth Studying.)

Diagnosis as to Cause.—1. Catarrhal icterus is a benign infectious form of hepatitis rather than, as was previously believed, merely an acute catarrhal cholecdochitis. It may occur in epidemics. It may be due to syphilis. Some believe that there may be an "emotional" form due to spasm of the sphincter of Oddi.

There may be initial fever and malaise, but the later course is afebrile. Nausea and vomiting with loose stools may appear before the jaundice. The feces are acholic at least for a time. The pulse is slow and the blood pressure low. Liver and spleen are moderately enlarged. The liver may be tender. Anemia with leukopenia and relative lymphocytosis follow the early leukocytosis.

The duration is usually three or four weeks, but it may be months. As it may exceptionally develop into the hepatosis type, the prognosis should be guarded.

2. Calculous icterus (see Cholelithiasis) sets in with or is preceded by paroxysms of colic or recurrent

High Carbohydrate, Low Fat and Low Protein Diet

Foods Which May Be Suitable in Cases of Obstructive Jaundice

Foods allowed:

Cereals	Any kind
Cereal products	Macaroni, spaghetti, vermicelli, noodles, bread, crackers
Fruits	Any kind; fresh fruit juices (such as orange juice, grapefruit juice or pineapple juice) should accompany each meal
Vegetables	Any kind except cabbage, onions, turnips
Cheese	Cottage
Beverage	Skim milk, buttermilk
Egg	Limit to one per day
Sweets	Sugar, jelly, jam, syrup, molasses, honey, candy (but not chocolates)
Desserts	Cornstarch, rice and tapioca puddings, gelatin desserts, angel food cake

Foods to avoid:

Pastries, gravies, fat meats and bacon, butter, mayonnaise and salad oils, nuts, cheese (except cottage cheese), cream, chocolate, olives

Sample Menu

Breakfast

Fruit juice, stewed fruit
Cereal with milk and sugar
Bread with jam
Coffee with milk and sugar

Dinner	Supper
Fruit juice	Fruit juice
Lean meat	Soup, crackers
Mashed potatoes	Cooked vegetables
Cooked vegetables	Soft cooked egg, one
Bread with jam	Bread with jelly
Stewed fruit	Tea
Skim milk	Dessert

febrile icterus, which may occur without pain. There is no gallbladder enlargement, but cholecystography is of no value in the presence of jaundice, as it prevents the excretion of the drug by the liver, and the dye may possibly be harmful. Roentgenography may reveal the presence of opaque stones.

3. Stenosis icterus, most commonly due to neoplasms when occurring in the later years of life, is probably malignant in nature. It lacks the distinguishing features of the other forms and is characterized most especially by its constancy, by its progressive character and by enlargement of the gallbladder.

4. Chronic pancreatitis (q. v.) presents the additional symptoms of absence of the external pancreatic secretion, and exceptionally there is glycosuria.

Note to House Physicians.—The admission of a jaundiced patient to the hospital demands the prompt application of tests to determine whether operation is indicated or not while the patient is gotten into the best possible condition for operation.

The urobilin test and the stercobilin test should be repeated daily, as only persistent absence for a week is surgically significant.

The liver function tests are the more valuable the earlier they are done and when repeated, because the insidious development of hepatosis may thus be detected.

Treatment.—1. General Regimen: It is best to confine the patient to absolute rest in bed for the first week or two even in apparently mild cases of jaundice, but after this period it is best, unless the patient is otherwise disabled, to have him get out of bed, as at this time exercise may favor earlier disappearance of the jaundice.

2. Diet: During the stage at which gastric symptoms dominate, the diet appropriate for the gastric condition should be chosen. As soon as the symptoms have abated, the chief principle of obstructive jaundice diet is the avoidance of fat, an abundance of carbohydrate and a limited amount of protein, preferably vegetable protein, being given.

3. Vitamin D: Because along with the failure of adequate fat digestion there no doubt goes inadequate absorption of vitamins A and D, it is claimed, though not proved, that lack of vitamin D, which makes calcium available for the body's use, may in part be responsible for the bleeding tendency of jaundiced patients (bleeding time, test 11). Solution of Irradiated Ergosterol (Viosterol) may therefore be given with possible advantage in 2 cc. doses three times a day, two hours after meals and accompanied by 0.5 Gm. doses of Extract of Ox Bile, best administered in double gelatin capsules to produce duodenal action so far as possible.

4. Vitamin C: It will be noted from the detailed dietary that administration of fruit juice is stressed because vitamin C deficiency is particularly prone to produce a tendency to capillary fragility (for test, see Hypovitaminosis C). Whenever achlorhydria is present —and it may be in jaundice—vitamin C is so extensively destroyed in the alimentary tract before it can be absorbed that parenteral administration of cevitamic acid is indicated and a daily dose of 0.6 Gm. should be aimed at until the urinary saturation test shows (see Hypovitaminosis C) that the systemic deficiency has been overcome.

5. Water Administration: Though also an item of diet, water administration needs particular stress placed on it because the cholemic factor of obstructive jaundice requires maximum attainable water diuresis to lessen itching and other symptoms of cholemia and to protect the kidneys against damage by the poisons they must excrete. The patient should therefore be encouraged to drink as much water as possible. Several additional advantages may be secured from large, cool enemas, of from 1 to 2 liters of tap water at 60 to 70 F. introduced slowly into the colon once or even twice a day and retained by the patient as long as possible. They aid in keeping the intestine clean; they may have a diuretic effect and, by diluting the urine, lessen the danger of nephritis; but most especially are they recommended because they are believed to be capable of increasing the flow of bile (choleretic action) and the temperature at which the injection is to be given is credited with being capable of reflex stimulation to evacuation of the gallbladder (cholagogue effect). No matter what the mode of action, they often help in relieving the pruritus of jaundice. (For the symptomatic relief see Therapy of Itching.)

6. Securing Bowel Evacuation: One should aim at obtaining at least one and not more than two bowel

evacuations a day. Phenolphthalein does not act in this condition. Cascara sagrada does.

(*a*) Cascara sagrada might be preferred as long as the patient is bedfast. It may be given at bed time in doses of from one to four teaspoonfuls of the Aromatic Fluidextract of Cascara Sagrada, enough to secure one or two bowel movements daily.

(*b*) A saline cathartic is likely to be useful when the patient is no longer bedfast. It is usually given combined with alkali on the supposition that alkali has a favorable effect on catarrhal inflammation of mucous membranes or, from an empirical standpoint, in an attempt at reproduction of the composition of Karlsbad water, which is famous in the treatment of diseases of the bile passages. Probably superior to the natural salt is the prescribing of a saline medicament of such composition as to meet the indications of the case. One may simply give the Effervescing Sodium Phosphate, 1 or 2 teaspoonfuls in one-half glassful of water one-half hour before the larger meals. If alkalization is also aimed at, one may prescribe Sodium Phosphate combined with Sodium Bicarbonate (prescription 1). If the phosphate is not sufficiently active, one may employ Sodium Sulfate (prescription 2) instead. Sodium Phosphate is preferred because less unpleasant to the taste.

PRESCRIPTION 1.—*Alkaline Saline Laxative*

℞ Sodium bicarbonate ..... 30 Gm.
Exsiccated sodium phosphate..... 60 Gm.
M. Label: Teaspoonful in cup of hot water one-half hour before the larger meals.

PRESCRIPTION 2.—*Alkaline Saline Purgative*

℞ Sodium bicarbonate ..... 30 Gm.
Exsiccated sodium sulfate..... 60 Gm.
M. Label: Teaspoonful in cup of hot water one-half hour before the larger meals.

(*c*) Mild Mercurous Chloride was used religiously in biliary disease by our forefathers in medicine on the supposition that it stimulated bile formation. It is now known that it does not do so but that it may possibly act as an intestinal antiseptic. For this purpose an occasional dose of mild mercurous chloride (prescription 3) given at bedtime may possibly be of advantage. It may add thoroughness to the evacuant therapy practiced. Continued, regular dosage is not admissible on account of the danger of mercurialism.

PRESCRIPTION 3.—*Mild Mercurous Chloride*

℞ Six tablets of mild mercurous chloride..... 0.06 Gm.
Label: One at bedtime as required.

7. Choleretic: Whether or not it is desirable to stimulate the secretion of bile in jaundice is a question still *sub judice*. One might imagine that such an effect might be desirable in catarrhal jaundice and also that increasing the bile pressure might possibly even help the passage of a small stone. Should such an effect be aimed at, Sodium Salicylate in doses of from 0.5 to 1 Gm. might be employed, and it may conveniently be added to the alkaline saline medication (prescription 4).

PRESCRIPTION 4.—*Choleretic Alkaline Saline*

℞ Sodium salicylate ..... 15 Gm.
Sodium bicarbonate ..... 30 Gm.
Exsiccated sodium phosphate..... 60 Gm.
M. Label: Teaspoonful in cup of hot water one-half hour before the larger meals.

8. Calcium: The hemorrhagic tendency of some jaundiced patients may possibly be antagonized by the administration of calcium, and this should always be given intravenously when a patient with increased clotting time is to be prepared for surgical intervention. To determine whether calcium will be of value in increasing the coagulability of the blood, the following test should be performed: Withdraw 2 cc. of blood by venipuncture. Set 1 cc. to coagulate spontaneously. To the other cubic centimeter add six drops of 0.5 per cent solution of calcium chloride. Determine the coagulation time (test 12) of both specimens. If the calcium containing specimen coagulates more rapidly, calcium is indicated; otherwise it is not.

(*a*) One may give 20 cc. of the 5 per cent solution of calcium gluconate by very slow intravenous injection at intervals of from four to six hours. Unfortunately the effect is transient and rather untrustworthy. Caution: Slough is liable to follow paravenous injection.

(*b*) If maximal effect from this form of therapy is aimed at, 25 units of Solution of Parathyroid may be given subcutaneously at twelve hour intervals for not more than a week. It may be renewed if necessary after an interval of a week.

9. Transfusion of Blood or of Blood Serum: This is the sheet anchor in jaundiced patients, even in cases of advanced hepatic disease, to lessen the bleeding tendency. As the cause of death after operation in these patients is hemorrhage in more than 50 per cent, routine preoperative blood transfusion should be mandatory, as it will usually control oozing at the time of operation.

Intramuscular injection of blood serum may suffice to increase coagulability when the number of red blood corpuscles is not markedly reduced. Blood serum should indeed be preferred, as the blood corpuscle destruction products increase the existing jaundice. It is only when there is a considerable degree of anemia present that the transfusion of 500 cc. of compatible whole blood answers best for the preoperative preparation of the patient. If human blood is not available, the intramuscular injection of horse serum or of diphtheria antitoxin may be resorted to.

10. Duodenal Tube Drainage: Drainage of the biliary system by means of the duodenal tube (nonsurgical drainage of the gallbladder) is useful chiefly as a diagnostic procedure, but it may also be of some value in preoperative preparation and as a possible therapeutic measure in cases in which operation entails an unwarranted hazard.

When the tube is in the duodenum and its contents have been drained, 50 cc. of a 33 per cent solution of magnesium sulfate at body temperature is injected, permitted to remain a while and then drained off for bacteriologic and cytologic examination. Another such quantity may be injected, but not more than 90 cc. should be permitted to be retained to avoid excessive purgative action. For patients suffering from diarrhea, a 5 per cent solution of peptone may be employed instead of the salt.

11. Surgical Operation: (*a*) In all cases of obstructive jaundice in which the obstruction is removable (calculi), in which no spontaneous tendency to improvement manifests itself within two weeks, operation should be undertaken as soon as the patient can be gotten into an operable condition.

(*b*) When the obstruction is irremovable (neoplastic), the earlier the operation the better the patient's chances to survive it.

(*c*) In the "catarrhal form" one should postpone operation as long as possible since jaundice of any kind makes all surgical interventions serious, but it must not be postponed too long in a persistent case, as operation

is the more serious the longer the jaundice has lasted. Drainage of the gallbladder is rarely advisable earlier than in the second month.

Tachycardia, oliguria, hemorrhagic symptoms and cachexia make surgery extremely hazardous and, in general, contraindicate it. The operative intervention should be limited to relieving the system of the dammed up bile. If the obstructive lesion can be removed easily and safely, this should be done; but, since safety to the patient is paramount, cholecystostomy should be performed when in doubt, with removal of the underlying cause later as the condition of the patient permits.

The following operations are available for the relief of obstructive jaundice:

(*a*) Cholecystostomy, indicated in cholelithiasis with cholangitis, and in catarrhal icterus of excessive duration.

(*b*) Choledochotomy for common bile duct stone that cannot be dislodged.

(*c*) Cholecystogastrostomy whenever there is nonremovable obstructive lesion of the common bile duct below the cystic duct.

PREOPERATIVE CARE OF GALLBLADDER CASES

Whenever possible, at least three or four days of preparation should be required. Bleeding (test 11) and clotting time (test 12) should be estimated daily so as to choose the optimum time for operation, and calcium infusion employed if indicated.

The patient's blood should be typed and suitable blood be made available as emergency postoperative blood transfusion may become imperative to save life.

Diet should include from 300 to 500 Gm. of carbohydrate daily. The eating of sweets should be encouraged. Syrup (150 cc.) in some flavoring fruit drink should be given the evening before and early the morning of the operation if the stomach is retentive. If it is not, dextrose phleboclysis (5 per cent) is mandatory.

Blood transfusion (500 cc.) should be given shortly before operation or if the red blood corpuscles are not required by marked anemia, human serum or horse serum should be injected intramuscularly.

POSTOPERATIVE CARE OF GALLBLADDER CASES

1. *Posture.*—In simple cholecystectomy any posture which is comfortable to the patient may be taken. In drainage cases, the sitting posture at an angle of about 35 degrees promotes drainage, as does Sims' posture.

2. *Phleboclysis.*—Dextrose (5 per cent) phleboclysis should be given for at least the first twenty-four hours. Salt solution should be administered if the urine shows a deficit of sodium chloride.

3. *Diet.*—Water may usually be allowed about six hours after operation. If vomiting persists, gastric suction (Wangensteen method) should be instituted, and parenteral fluid administration is indicated. After twenty-four hours, if the intestine has not been subjected to operation, a residue-low diet (q. v.) may be started.

4. *Insulin.*—Administration of insulin (from 15 to 20 units a day) plus an adequate amount of sugar may be advisable during the second week postoperatively to combat the asthenia with anorexia and resulting emaciation, which may result in death. The insulin may antagonize the anorexia and the better utilization of the sugar combat the malnutrition.

5. *Pain.*—Pain indicates nitrite administration (Amyl Nitrite inhalation, a few whiffs, or Glyceryl Trinitrate 0.6 mg.) may be superior to hypodermic injection of Morphine, as pain due to biliary colic sometimes troubles these patients and morphine increases while nitrite releases spasm of the sphincter of Oddi.

6. *Hemorrhage.*—This symptom or even capillary oozing indicates blood transfusion, repeated as required.

7. *Biliary Infusion.*—The McArthur drip method, by way of bile drainage tube or bile fistula of from 500 to 3,000 cc. of warm sterile dextrose solution (with salt if there is a deficit of sodium chloride), is indicated in persistent postoperative vomiting and in cases associated with toxic nephritis. The biliary drainage tube is attached to an irrigator the outflow of which is so adjusted as to deliver the fluid drop by drop. The height of the irrigator does not exceed 20 inches above the patient's abdomen. If pain is experienced, the rate of flow should be lessened. If this does not relieve the pain there is obstruction to the entrance of fluid into the duodenum.

8. *Cholangiography.*—Roentgenography after injection of from 10 to 20 cc. of contrast medium (hippuran or diodrast) into the bile passages enables one to decide how long the biliary tree should be drained. Patency of the common bile duct may thus be confirmed. Indeed the injection may help to flush out small stones, sand, or mucous plugs.

9. Complicating acidosis, alkalosis, hepatic or renal insufficiency or peritonitis must be looked out for and appropriate treatment for these must be instituted should any of these appear.

E. HEPATOSIS ICTERUS, ICTERUS GRAVIS, TOXIC JAUNDICE

Hepatosis icterus, icterus gravis or toxic jaundice is due to acute functional liver insufficiency resulting from extensive degeneration of liver cells, such as may result from phosphorus or cinchophen poisoning, or occur in acute yellow atrophy of the liver, yellow fever, spirochetosis icterohaemorrhagica (Weil's disease) or congenital syphilis (rare), and as a terminal event in hepatic cirrhosis.

Diagnosis.—Malaise, epigastric pain and tenderness, nausea and vomiting are followed by jaundice, which is subordinate to the constitutional symptoms, hemorrhages from the gastro-intestinal tract, evidences of nephritis and finally stupor, coma and death. The excretion of bile, while augmented at first, may later cease, so that light colored or even acholic stools may result.

In addition to other liver function test methods (tests 5, 8 and 9) the finding of tyrosinuria indicates liver degeneration.

Treatment.—1. Causal treatment should, of course, be aimed at and a diagnosis of the underlying etiology arrived at as expeditiously as possible.

2. Absolute rest is imperative.

3. The therapeutic value of dextrose phleboclysis in jaundice cannot be overestimated. Numerous observers agree that intensive dextrose therapy is of first importance and that other measures are only adjuvants in these cases. It must be given intravenously, as then the glycogen is deposited in the liver more liberally than when the sugar is taken by mouth. Drip phleboclysis of 10 per cent dextrose solution should aim at giving the patient from 300 to 500 Gm. in the twenty-four hours and enough salt should be introduced to maintain at least 0.3 per cent excretion of sodium chloride in the urine.

4. Diet consists of the ingestion of carbohydrate. The eating of candy should be encouraged. Protein should be limited to the basal requirement and in critical conditions temporarily withheld.

5. Insulin should be given to those patients who receive large amounts of dextrose and in whom hyperglycemia develops, or who spill sugar in the urine. The proportion of 1 unit of insulin to every 3 Gm. of dextrose lost is advisable.

6. Blood transfusions are especially indicated when jaundice is complicated by purpura, anemia, spontaneous hemorrhages, low serum protein and failure to show gain on dextrose therapy alone.

F. ICTERUS OF THE NEW-BORN

It is important to differentiate between (1) the mild and (2) the grave form of icterus of the new-born.

1. In the mild form, prognosis is good.

(*a*) Icterus neonatorum is so common, occurring in almost 80 per cent of infants on the first or second, rarely the third or fourth day, that it may almost be called "physiologic jaundice." It is usually a subicterus, as the urine is normal, but it may become a hyperhemolysis icterus. There are no other symptoms. It requires no treatment.

(*b*) Catarrhal icterus with biliuria, acholic stools and slow pulse is very rare in the new-born. The principles of treatment are the same as those employed in older children.

2. In the grave form prognosis is bad.

(*a*) Obstructive icterus may be due to congenital syphilis and require its specific therapy, or to congenital malformations or gallstones (rare) and require surgical intervention.

(*b*) Hepatosis icterus (icterus gravis neonatorum) may be due to infection through the umbilicus and appear in epidemics. Its occurrence is favored by bathing infants before the site of the umbilical cord has healed, but the infection may also be intestinal in origin. It sets in about the fifth day of life with fever and rapid pulse, vomiting and diarrhea, hemorrhages, bronzed skin and restlessness. When the patient passes into coma it usually ends in death.

The principles of treatment are the same as in icterus gravis of adults. Antistreptococcus serum may be tried in infection of the umbilical cord.

(*c*) Grave familial jaundice may be an exaggerated form of the physiologic icterus. Intramuscular injection of the mother's blood serum may help.

TESTS THAT MAY BE OF USE IN JAUNDICE CASES

A. *Test made on the feces:*

TEST 1.—*Test for Stercobilin (Schmidt's Stool Bile):* Reagent: Saturated aqueous mercury bichloride solution.

Procedure: Rub a small amount of fecal material with mercury bichloride solution and let stand for twenty-four hours. The work is conveniently carried out in small beaker, evaporating dish or watch glass. Urobilin, which is present normally in the feces, gives a red color. A green color is given by unchanged bilirubin, which is not seen normally.

B. *Tests made on the urine:*

TEST 2.—*Urobilinogen:* Urobilin (excreted as the chromogen urobilinogen) is normally present in the urine in too small an amount for detection by the ordinary tests. Its quantity is increased in conditions in which there is (*a*) excessive destruction of red blood corpuscles, as in hemolytic jaundice, pernicious anemia, malaria; (*b*) when the oxidizing function of the liver is impaired, e. g., by cirrhosis, poisons (arsphenamine, phosphorus, lead), congestions and in infectious diseases. Urobilinuria is nearly or entirely absent in obstructive jaundice. Provided hemolysis can be excluded, a positive reaction is of great value, indicating impairment of hepatic function. Temporary urobilinuria may be caused by constipation.

Test for Urobilinogen (Ehrlich's Modified): Reagent: 2 Gm. of paradimethylamidobenzaldehyde in 100 cc. of 20 per cent hydrochloric acid.

Procedure: (It is best to use individual specimens rather than a mixture of a twenty-four hour quantity). To 10 cc. of urine, add ten drops of reagent. Add 3 or 4 cc. of chloroform. Hold a finger over the top of the tube or stopper with a cork and mix thoroughly by holding the tube horizontally and with a slow motion moving tube back and forth. Let the chloroform settle to the bottom.

Result: A pink to red color develops in the chloroform layer in the presence of urobilinogen. A yellowish color is not significant.

TEST 3.—*Test for Bilirubinuria (Gmelin Test):* Reagents: Calcium hydroxide (10 per cent) or lime water. Be sure the lime water is active. Concentrated yellow nitric acid.

Method: To from 10 to 15 cc. of urine add sufficient lime water to form firm precipitate of calcium salts. Such will have carried down by adsorption any bile pigments which may be present. Filter and lay filter paper containing the precipitate on a flat surface. Touch the precipitate lightly with a drop of nitric acid, using either a glass rod or a dip tube. A play of colors from yellow through green to violet denotes the presence of bile pigments.

TEST 4.—*Tests for Bile Acids (Choluria):* Hay's Test: This test depends on the fact that bile acids lower the surface tension of the urine. It is delicate to a dilution of 1:120,000.

Reagent: Finely divided and dry sublimed sulfur.

Procedure: On surface of 10 cc. of urine cooled to below 17 C. sprinkle some finely divided sulfur. Note whether the sulfur sinks or not, and also the rate of sinking. Preservation with thymol interferes with this test.

Furfurol Test: Reagent: 1:1,000 aqueous solution of furfurol. Concentrated sulfuric acid.

Procedure: To 5 cc. of urine add three drops of furfurol solution. Holding the tube on a slant, carefully run about 5 cc. of sulfuric acid down the side. Note the junction of the two liquids. In presence of bile acids a red ring develops. Care should be taken not to let tube become too hot (over 70 C.).

TEST 5.—*Galactose Tolerance Test:* This test has the advantage of not requiring venipuncture, but one must rule out presence of concomitant diabetes mellitus. Collect specimen of urine between one and two hours after an ordinary meal on the day preceding the galactose test. If the patient has any tendency toward diabetes, dextrose will be found in this specimen, unless there is a high renal threshold. If this is so, at least there will be no dextrose present in the urine to interfere with the galactose test. As galactose has no renal threshold, a high threshold for dextrose does not interfere. If the patient has diabetes, the dextrose will have to be eliminated from the urine by means of fermentation with pure yeast.

Reagents: Galactose, chemically pure, 40 Gm. in 500 cc. of water. It may be flavored with lemon juice to make it more palatable. Benedict's reagent. Sodium carbonate crystals. Powdered pumice.

Procedure: Patient should have no breakfast. Obtain a specimen of urine. Give the patient the galactose solution to drink. Collect specimens hourly for the next five hours and record the quantity having been previously eliminated; any reducing sugar present can be assumed to be galactose. Pool those specimens showing reduction and determine the amount of galactose quantitatively.

Dilute 10 cc. of urine to 50 cc. with water. This should be done volumetrically so that the dilution is accurate. Mix thor-

oughly and pour into a buret. Place 25 cc. of Benedict's reagent in a large evaporating dish (measure with a pipet or if the pipet is not large enough use a buret). Add 15 Gm. of crystallized sodium carbonate and a few grams of powdered pumice. Heat to boiling until the carbonate has entirely dissolved. Take a reading before urine is discharged into copper solution, then run in diluted urine rapidly until a white chalky precipitate forms. From that point add urine drop by drop until the color has entirely disappeared and note the number of cubic centimeters of urine used. Keep the solution boiling vigorously during the procedure.

Calculation: Twenty-five cc. of solution is neutralized by 67 mg. of galactose. Therefore the number of cubic centimeters of urine needed to decolorize the solution contained 67 mg. of sugar, but the specimen was diluted five times and therefore $\frac{0.067 \times 500}{x}$ = percentage of urine present in pooled specimen. From the percentage of galactose eliminated, determine the number of grams by calculating the actual number of cubic centimeters of urine that made up the pooled specimen. Thus, if a patient voided 150 cc. and the result of the determination gave 3 per cent, the patient would have eliminated 4.5 Gm. of galactose in the 150 cc. of urine.

Interpretation: An output of 3 Gm. or above is abnormal and speaks for liver damage. The average urinary output of galactose is less than 1 Gm., and it usually appears in the first and second specimens in normal persons. In obstructive jaundice the output is less than 3 Gm., so that the test is of little value in this type of jaundice; but in hepatosis jaundice it is more than 3 Gm.

This test is of no value as a general liver function test but is invaluable in the differential diagnosis of jaundice, especially if made early. It is of greatest value in painless jaundice of middle and later life and may prevent unnecessary surgery in hepatosis jaundice.

C. *Tests made on the blood:*

TEST 6.—*Icterus Index Estimation:* This depends on the intensity of yellow pigment of the serum compared with a standard aqueous potassium bichromate solution (1:10,000) and reported in arbitrary units, expressed as the icterus index. The normal range is between 4 and 6; subicterus or "latent jaundice" up to 15. Beyond this figure the patient usually shows evidence of true icterus. In cases of obstructive jaundice there may be from 150 to 200 units, and it may be extremely high from 300 up in cases of hepatosis jaundice.

Reagents: A 1:10,000 aqueous potassium dichromate. Physiologic solution of sodium chloride. Six test tubes of the same caliber.

Procedure: Measure 1 cc. of serum in a pipet. Dilute with a measured amount of physiologic solution of sodium chloride until nearly the color of the standard. Compare this diluted unknown against the standard in a suitable colorimeter.

Calculation: $\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \text{dilution of unknown} = \frac{\text{icterus}}{\text{index}}$

TEST 7.—*Van den Bergh Test (Qualitative Test, Modified):* There are several types of reactions. We are concerned here with only the direct reaction. The direct reaction is either immediate or delayed. The immediate reaction develops as soon as the reagent is added to the serum. The delayed reaction does not begin until after thirty seconds and may not reach its maximum color until after two or more minutes. An immediate red color becoming deep violet points to an obstructive jaundice. Delayed reactions may be given by normal serums and those of hepatosis jaundice. The reaction is negative if no color develops within thirty minutes. Occasionally serums from patients with obstructive jaundice fail to reach their maximum before two or more minutes has elapsed. Serums from patients with toxic or infective jaundice usually reach their maximum after thirty seconds.

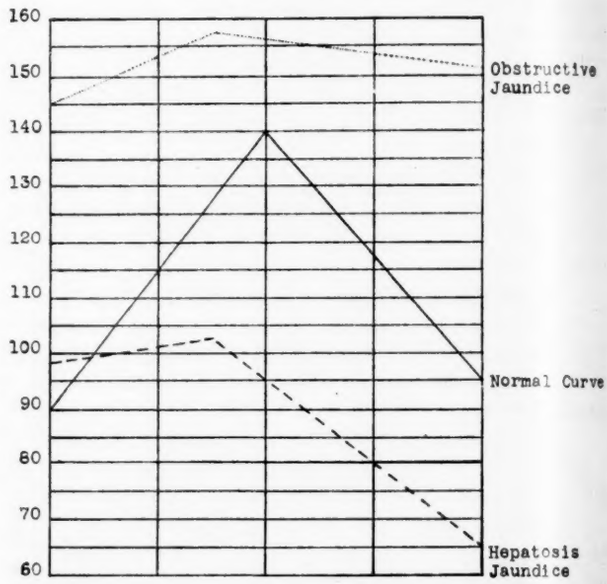
Reagents: Solution 1. Sulfanilic acid 1 Gm., concentrated hydrochloric acid 15 cc., distilled water to 1,000 cc.

Solution 2. Sodium nitrite 0.5 Gm., distilled water to 100 cc.

To prepare fresh reagent add 5 cc. of solution 1 to two drops of solution 2.

Procedure: Draw approximately 6 to 8 cc. of blood. Allow to clot, centrifugating if necessary. Pipet off the serum and measure accurately with a graduated pipet 1 cc. into a clean dry test tube. Add 1 cc. of freshly prepared reagent. Note the development of color. Watch the time of development of color, so that the time taken for development can be reported accurately.

TEST 8.—*Dextrose Tolerance Test:* The patient should have no breakfast. A specimen of blood of the fasting patient is drawn, and then the patient is given 100 Gm. of dextrose dissolved in 200 cc. of water. Since dextrose dissolves slowly and possibly must first be heated, it must be prepared in advance. The juice of one lemon added to the solution will make it more palatable. Forty-five minutes after ingestion of the dextrose another specimen of blood is drawn. A third specimen is obtained two hours after the ingestion of the dextrose. Note: Oxalated blood is used for this determination. The specimens should be kept in a refrigerator until the determinations are made so as to avoid hemolysis. A curve should then be plotted and compared with those given in the accompanying chart.



Normal curve and curves characteristic of obstructive jaundice and hepatosis jaundice.

If the curve of obstructive jaundice is obtained, diabetes mellitus must be ruled out, as it may give a similar curve. The fasting blood sugar may be high in a well developed case of diabetes, but one cannot take for granted that a result on the fasting blood within normal limits indicates absence of a diabetic state.

TEST 9.—*Cholesterol Estimation:* This is of differential value, as the liver removes cholesterol from the blood and excretes it in the bile. In obstructive jaundice the cholesterol content is high (from 300 to 400 mg.), in liver degeneration it is normal (from 130 to 170 mg.) or it may be markedly decreased (grave prognosis). High values are also found in nephrosis, diabetus mellitus in which recent treatment with insulin has not been given and after diets high in lipoids.

Oxalated blood is used for this test. Draw about 5 cc. of blood. The cholesterol is determined by extracting the lipoids by means of ether-alcohol mixture. The extract is saponified and the cholesterol is then extracted by chloroform. The freed cholesterol is determined quantitatively by the colorimeter.

Procedure: Into a 50 cc. volumetric flask put about 40 cc. of ether and alcohol mixture (ether 1 part, alcohol 3 parts), add 1.5 cc. of oxalated blood and keep the flask in motion while it is being added. Immerse the flask in boiling water until its contents reach the boiling point (six or seven seconds). Keep the flask in motion all the time it is in the boiling water. Avoid overheating. Cool and add alcohol mixture to the

50 cc. mark. Mix and filter. Transfer 10 cc. of filtrate to a beaker and evaporate over a water bath to nearly dryness, keeping the beaker level; then add 2 cc. of chloroform. Heat to boiling and transfer to a 10 cc. graduated cylinder. Add 2 cc. of chloroform. Heat to boiling. Transfer to the same cylinder. Repeat the third time. If the three portions exceed 5 cc., evaporate to 5 cc.; if less, add enough chloroform to make 5 cc.

Into a 10 cc. graduated cylinder put 5 cc. of Standard Cholesterol Solution. To each cylinder add 2 cc. of anhydrous acetic acid and 0.1 cc. of concentrated sulfuric acid. Mix and place in the dark for from six to eight minutes. Compare colors in the colorimeter.

Calculation: The standard is set at 15. Twenty-five hundred divided by the reading of the unknown gives the number of milligrams of cholesterol in 100 cc. of blood. Note: Be sure that every pipet, tube and beaker is very dry.

TEST 10.—*Fragility of Red Cells (Sanborn Modification):* Reagents: 0.5 per cent sodium chloride solution made from freshly dried chemically pure sodium chloride.

Procedure: Label twelve small test tubes (be sure the tubes are of the same caliber) from 25 to 14 inclusive. With a capillary pipet put into each tube the number of drops of stock sodium chloride solution indicated by the number on the tube; i.e., twenty-five drops in tube 25 down to fourteen drops in tube 14. Then wash out the pipet carefully with distilled water. Using the same pipet, bring up the volume of fluid in each tube to twenty-five drops with distilled water. Draw blood from the patient by means of venipuncture into a dry syringe, taking from 1 to 1.5 cc. Transfer a drop of blood immediately to each tube. (For accurate results the same caliber needle should always be used; a No. 21 is convenient.) Mix by inverting the tubes carefully so as not to fracture red cells artificially. Let stand at room temperature for two hours and read the results.

Results: Corpuscles will have settled to the bottom and any hemolysis is noted by discoloration of the supernatant fluid. The reading is taken in the tube showing the slightest amount of color.

Calculation: Multiply the number indicated on the tube by 0.02.

Interpretation: Normal blood hemolyzes at from 0.42 to 0.44 concentration of sodium chloride, although a variation between 0.02 and 0.04 is considered to be within normal limits. Increased fragility is seen in hemolytic jaundice, which shows complete hemolysis at 0.48 Chronic obstructive jaundice shows no abnormality of hemolysis. In pernicious anemia there is increased resistance.

TEST 11.—*Bleeding Time Determination (Ivy Technic):* The cuff of a sphygmomanometer is applied around the arm with a pressure of 40 mm. of mercury. Puncture on the inner side of the forearm is performed with a mechanical stylet set at a depth of about 2.5 mm. and drops of blood are taken on filter paper every ten seconds until the bleeding has stopped. This is determined by the fact that no red blot is formed on the paper when the site is touched with the paper. Be careful to avoid fallacies produced by small amounts of blood gathering about the site of the puncture. It is best to wipe such away between times that tests are made. Count the number of blots on the paper. Multiply by 10. This will give the bleeding time in seconds.

TEST 12.—*Coagulation Time (Peterson and Mills, 1923):* Capillary tubes (from 0.6 to 0.8 mm. inside diameter and 1¼ inches in length) are filled by capillarity up to about one-quarter inch from the end. Puncture like that used in test 11 is the method of obtaining blood, excepting that no tourniquet is needed. The filled tube is immediately placed in one of the creases of the palm of the examiner's hand and the hand is closed over it. Coagulation is recognized by failure of the blood column to move within the tube when it is inverted by pronation and supination of the hand momentarily opened to permit inspection. If such observation is doubtful, a small piece of the tube may be broken off, and if a firm clot has formed a strand of fibrin will extend between the broken off portion and the remainder of the blood. Determine the number of seconds from the time the puncture is made until the final results are read.

ADDITIONAL LIVER FUNCTION TESTS WORTH STUDYING

Phosphatase Test (Robert's, Modified): Tests are to be made on fasting blood. Citrated blood is to be used. Oxalated blood cannot be used because potassium oxalate is usually used. Be careful of this: if citrate is not handy then sodium oxalate can be used. About 10 cc. of blood should be taken and immediately transferred to a container with anticoagulant. The test is made on the plasma, so here too care must be used to avoid hemolysis. The amount of inorganic phosphorus is determined before and after the action of phosphatase enzyme and the amount of phosphatase is then reported in units per hundred cubic centimeters of blood.

Procedure: Two cubic centimeters of plasma (citrated blood) is mixed with 2.3 cc. of distilled water and 0.7 cc. of tenth normal sodium hydroxide. This produces a p_H of approximately 8.9. To this is added 1 cc. of a 1 per cent solution of sodium beta-glycerophosphate. The mixture is then incubated at 37.5 C. for two hours, after which its inorganic phosphorus content is determined by the method of Fiske and Subbarow.[2] At the same time the initial inorganic phosphorus content of the plasma is determined, another 2 cc. of the original blood being used. Both of these values are determined in milligrams per hundred cubic centimeters of blood plasma. The difference between these two values represents the number of milligrams of inorganic phosphorus liberated by the enzyme phosphatase from the substrate under the foregoing conditions. Each milligram thus obtained is expressed as units of phosphatase per hundred cubic centimeters of blood plasma.

Albumin-Globulin Ratio Determination: Nonobstructive jaundice shows a low serum albumin and a high serum globulin. In some cases an inversion of the albumin-globulin ratio may occur. No apparent change in this ratio occurs in cases of obstructive jaundice.

Hippuric Acid Test and Urea Clearance Test (Dr. Quick): This is valuable as a prognostic agent in determining the amount of liver damage (such is not always commensurate with the degree of jaundice present), especially when hepatobiliary surgery is contemplated, as "liver deaths" can thus be avoided. The test is valuable also in determining the amount of liver damage caused by syphilis and in the differential diagnosis between acute arsenical hepatitis and syphilitic hepatitis.

This test depends on the fact that glycol has the power to conjugate noxious substances in the liver (early thought to be a function of the kidneys), and so the detoxifying power of the liver can be determined.

Procedure: The patient is given 5.9 Gm. of sodium benzoate in half a glassful of water at 8 a. m. Breakfast is limited to coffee and plain toast. Specimens of urine are collected at hourly intervals for the next four hours. The amount is measured and then pooled.

2. Fiske, C. H., and Subbarow, Yellapragada, J. Biol. Chem. **66**: 375 (Dec.) 1925.

Because the excretion of hippuric acid does have a renal threshold, it is necessary to make a urea clearance test (van Slyke method) on the urine at the time the hippuric acid test is made. Unless the urea clearance is less than 20 per cent of the normal, there will be no interference with the hippuric acid excretion.

Tyrosinuria and Tyrosinemia: Tyrosine and leucine are usually found together in the urine. They may be present [3] in cases of liver damage, especially phosphorus poisoning, in acute yellow atrophy and also in leukemias.

Council on Physical Therapy

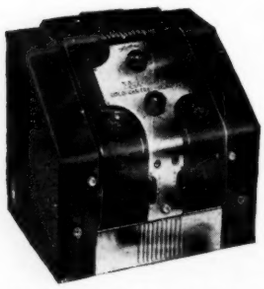
THE COUNCIL ON PHYSICAL THERAPY HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT:

H. A. CARTER, Secretary.

WAPPLER COLD CAUTERY-SCALPEL ACCEPTABLE

Manufacturer: Comprex Division, American Cystoscope Makers, Inc., 450 Whitlock Avenue, New York.

The Wappler Cold Cautery-Scalpel is a portable electrosurgical unit designed to provide power for electrosurgical procedures as well as to supply light for diagnostic instruments. It is recommended by the firm for such surgical measures as coagulation, cautery, cutting, including underwater cutting, hemostasis and cervical conization.



Wappler Cold Cautery-Scalpel.

Housed in a black bakelite case with chrome trim, the unit fits into a leather case with zipper and pocket for footswitch. It weighs 13 pounds and the dimensions are approximately 7 by 7 by 8 inches. Two distinctive features are (1) a drawer, serving also as a sterilizing tray, which works automatically at the press of a button, and (2) self-contained cords, similarly operated, which retract inside the unit. A single control knob permits the selection of the type of current for the effect desired. Several sets of bipolar electrodes are available. For sterilization, the drawer and contents may be placed in an autoclave or boiled. A foot switch operates the surgical current while the diagnostic light current is used independently.

Electrosurgical current is supplied by a vacuum tube circuit. The diagnostic light circuit is designed to operate lamps simultaneously with surgical current and from the same source eliminating the batteries commonly required with cystoscopic instruments. It operates at 110 volts, 50-60 cycle alternating current. The power input is 250 watts maximum. No value is given for output, since no reliable means for measuring this value has been decided on. The transformer temperature rise after a two hour run on intermittent load was within the limits of safety.

The unit was tried out clinically by an investigator appointed by the Council and reported to be satisfactory for general surgical work. However, it does not appear to produce a true desiccating current. Even when the current is cut down to a small amount and used with only a small needle, it causes coagulation rather than desiccation.

In view of the foregoing report, the Council on Physical Therapy voted to accept the Wappler Cold Cautery-Scalpel electrosurgical unit for inclusion in its list of accepted devices.

3. Presence is determined by the method described in the following articles:
Lichtman, S. S., and Sobotka, Harry: An Enzymatic Method for the Detection of Tyrosine in the Urine, J. Biol. Chem. **85**: 261 (Dec.) 1929.
Jankelson, I. R.; Segal, M. S., and Aisner, Mark: Tyrosinemia and Its Relation to Pathology of the Liver, Am. J. M. Sc. **193**: 241-246 (Feb.) 1937.

Council on Pharmacy and Chemistry

REPORT OF THE COUNCIL

BECAUSE OF STATEMENTS WHICH HAVE BEEN MADE IN THE ADVERTISING OF SEDORMID, THE COUNCIL DEEMS IT NECESSARY TO PUBLISH A REPORT ON THIS PREPARATION. A COMPETENT PHARMACOLOGIST WAS CONSULTED BECAUSE OF HIS SPECIAL KNOWLEDGE OF THIS SUBJECT. THE COUNCIL'S REFEREE EXAMINED THE STATEMENT PREPARED BY THE CONSULTANT AND THE ADVERTISING WHICH WAS AVAILABLE TO HIM. THE STATEMENT OF THE CONSULTANT IS TOO LONG FOR PUBLICATION IN FULL, BUT THE COUNCIL ADOPTED AN ABSTRACT OF THAT STATEMENT AND AUTHORIZED ITS PUBLICATION; AT THE SAME TIME THE COUNCIL DECLARED SEDORMID NOT ACCEPTABLE FOR NEW AND NONOFFICIAL REMEDIES BECAUSE OF THE CLAIMS WHICH THE COUNCIL HOLDS TO BE UNWARRANTED.

PAUL NICHOLAS LEECH, Secretary.

SEDORMID NOT ACCEPTABLE FOR N. N. R.

In this issue of THE JOURNAL (p. 725) Hoffman, Kahn and Fitzgibbon discuss work on Sedormid, which is referred to in this report. There also appears in this issue a clinical note by Moody (p. 726).

Sedormid (dormire, Latin, to sleep) is the therapeutically suggestive name of a sedative and hypnotic drug marketed by Hoffmann La-Roche, Inc.

The referee has examined seventeen pieces of advertising for Sedormid. Fourteen of these were received in the Council's office during the years 1930-1936; three are found in the *Roche Review* for 1937. The referee finds little essential change in the general character of the advertising for those years. Certain objectionable statements are assembled in order to facilitate their consideration. Naturally, those statements which do not require criticisms are not included. Not one word of warning to indicate that the use of Sedormid involves the least danger was found in these seventeen pieces of advertising; on the contrary, an advertising circular which the Council office received Oct. 1, 1935, contains the following:

"As a hypnotic, Sedormid is indicated in all cases of insomnia regardless of the cause of the sleeplessness."

"Sedormid is a carbamide, and is not affected by legislation aimed solely at barbiturates, . . ."

"It is non-cumulative, even when taken regularly for long periods."

"Sedormid is an unusually safe sedative and hypnotic, producing its therapeutic effects in doses far below the possibility of toxicosis. It is very quickly and completely oxidized in the body and is rapidly eliminated, so that even after large doses only traces are found in the urine the day after administration. Cumulative effects are, therefore, entirely absent."

"As a daytime Sedative . . . Bromides, in ordinary doses, are too weak; barbiturates are too strong; Sedormid, neither a bromide nor a barbiturate, meets the indication precisely."

The *Roche Review*, May 1937, states: "Its action while mild, is prompt, and in therapeutic doses its toxicity is practically nil."

It is stated many times in the advertising that Sedormid is neither a bromide nor a barbiturate, but a carbamide. It may, in fact, be considered a derivative of alurate, one of the most active of the barbiturates in general use. Alurate is allyl-isopropyl-barbituric acid; Sedormid is allyl-isopropyl-acetyl-carbamide. Its pharmacologic and therapeutic actions resemble those of the barbiturates.

It is obvious that no single hypnotic is "indicated in all cases of insomnia, regardless of the cause of the sleeplessness"; that suitable doses of barbiturates are not too strong; that suitable doses of bromides are not too weak; that therapeutic doses of barbital are not toxic, since the therapeutic excludes the toxic, though, of course, doses usually used therapeutically may cause toxic effects in some patients, especially when they are given in unsuitable cases. The paper on Sedormid which appears in this issue of THE JOURNAL affords abundant evidence that Sedormid, like one of the barbiturates, may cause toxic effects.

There are only two recent reports of experimental studies of Sedormid with which the referee is acquainted. Fromherz [1] investigated the spasmolytic action on excised strips of rabbit intestine and uterus, and frog ventricle. Fromherz drew no important deductions from this work with reference to therapeutic uses of Sedormid.

1. Fromherz, K.: Arch. f. exper. Path. u. Pharmakol. **173**: 78, 1933.

Gatti[2] determined the hypnotic, sedative and fatal doses of Sedormid for rabbits and guinea pigs. His report is not sufficiently detailed to permit of a satisfactory analysis. Of greater practical importance for the present report are the results of experiments performed under the direction of the consultant of the Council; in these experiments intramuscular doses of 0.1 Gm. of Sedormid per kilogram were fatal to pigeons but were without demonstrable effects when such doses were administered to rabbits. Doses of one fourth of the fatal dose caused only slight depression in pigeons.

Fontanier[3] reported fatal poisoning by fifty-one tablets (12.75 Gm.) of Sedormid, the amount being equal to the average fatal dose of barbital for man. The symptoms were closely similar to those seen in fatal barbital poisoning and included unconsciousness, rapid and stertorous respiration, irregular and intermittent pulse of increased frequency, miosis, abolition of the corneal reflex, increased temperature and, later, bronchopneumonia. The histologic changes in the central nervous system were identical with those observed after fatal barbital poisoning.

Verbiest[4] reported severe poisoning in a patient of 50 who had taken twenty tablets containing about 5 Gm. of Sedormid. There was unconsciousness, with cardiac weakness requiring active treatment, followed by complete recovery in three days.

Six observers have reported eleven (possibly twelve) cases of thrombopenic purpura following the use of repeated small doses of Sedormid. It is not necessary to discuss these further in this place, since several of them are discussed by Hoffman, Kahn and Fitzgibbon in this issue of THE JOURNAL.

The Council declared Sedormid (Hoffmann La-Roche, Inc.) unacceptable for New and Nonofficial Remedies because of the dangerously misleading statements in the advertising (conflict with Rule 6), and authorized the publication of this report.

NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

PAUL NICHOLAS LEECH, Secretary.

NEOARSPHENAMINE-D. R. L. (See New and Nonofficial Remedies, 1937, p. 86).

The following additional dosage form has been accepted:

Neoarsphenamine and Metaphen-D. R. L.: Packages containing five ampules of neoarsphenamine-D. R. L., 0.04 Gm. each, and one bottle (20 cc.) of metaphen solution 1:1,000.

Actions and Uses.—Neoarsphenamine and metaphen is proposed for the treatment of Vincent's gingivitis and stomatitis.

Dosage.—Neoarsphenamine 0.04 Gm. is diluted with 4 cc. of the 1:1,000 aqueous solution of metaphen and the resultant solution is applied topically.

CONCENTRATED POLLEN ANTIGENS-LEDERLE (See New and Nonofficial Remedies, 1937, p. 35).

Mixed Grasses Concentrated Pollen Antigen-Lederle (June Grass, Orchard Grass, Sweet Vernal Grass, Red Top and Timothy, in equal parts): Also marketed in five syringe packages (series D), each syringe containing 3,000 pollen units; and in five syringe packages (series E), each syringe containing 6,000 pollen units.

METAPHEN (See New and Nonofficial Remedies, 1937, p. 295).

The following dosage form has been accepted:

Metaphen Ophthalmic Ointment: Metaphen 1:3,000 in an ophthalmic ointment base containing anhydrous wool fat 25 per cent and petrolatum 75 per cent.

POLLEN ANTIGENS-LEDERLE (See New and Nonofficial Remedies, 1937, p. 37).

Mixed Grasses Pollen Antigen-Lederle (June Grass, Orchard Grass, Sweet Vernal Grass, Red Top and Timothy in equal parts): Also marketed in five syringe packages (series D), each syringe containing 3,000 pollen units; and in five syringe packages (series E), each syringe containing 6,000 pollen units.

MERCURIC SUCCINIMIDE (See New and Nonofficial Remedies, 1937, p. 288).

Ampoules Mercury Succinimide 0.01 Gm. (⅙ grain): Mercuric succinimide-U. S. P., 0.01 Gm., in distilled water to make 1 cc.
Prepared by the Lakeside Laboratories, Inc., Milwaukee.

2. Gatti, G.: Note e riv. di psichiat. **61:** 465 (Sept.-Dec.) 1932.
3. Fontanier: Ztschr. f. d. ges. Neurol. u. Psychiat. **152:** 494, 1935.
4. Verbiest, H.: Nederl. tijdschr. v. geneesk. **79:** 2533 (May 25) 1935.

Council on Foods

ACCEPTED FOODS

THE FOLLOWING PRODUCTS HAVE BEEN ACCEPTED BY THE COUNCIL ON FOODS OF THE AMERICAN MEDICAL ASSOCIATION AND WILL BE LISTED IN THE BOOK OF ACCEPTED FOODS TO BE PUBLISHED.

FRANKLIN C. BING, Secretary.

GOLDEN GATE BRAND MACARONI PRODUCTS

Manufacturer.—Golden Gate Macaroni Company, Inc., San Francisco.

Description.—Macaroni of various sizes and shapes prepared from durum wheat semolina.

Manufacture.—The sifted durum semolina and water, in definite proportions, are mechanically mixed and kneaded. The resulting dough is forced through various dies to form the different shapes of macaroni products, which are dried on racks under controlled conditions and packed in cellophane bags.

Analysis (submitted by manufacturer).—Moisture 13.4%, total solids 86.6%, ash 0.6%, fat (ether extract) 0.2%, protein (N × 5.7) 13.3%, reducing sugars as dextrose 0.7%, sucrose 1.7%, crude fiber 0.2%, carbohydrates other than crude fiber (by difference) 72.3%.

Calories.—3.4 per gram; 97 per ounce.

LESLIE BRAND IODIZED TABLE SALT

Manufacturer.—Leslie Salt Company, San Francisco.

Description.—Table salt containing 1 per cent magnesium carbonate and 0.02 per cent potassium iodide.

Manufacture.—Salt brine is obtained from sea water by spontaneous evaporation in ponds. The crude salt is washed with saturated salt solution to remove other soluble salts, then refined by dissolving in distilled water and precipitating out salts other than sodium chloride, and dried. Magnesium carbonate and potassium iodide are added and the salt is packed in cartons.

Analysis (submitted by manufacturer).—Moisture 0.01%, silica and iron oxide (SiO_2&Fe_2O_3) trace, calcium sulfate ($CaSO_4$) 0.01%, calcium carbonate ($CaCO_3$) 0.08%, basic magnesia ($Mg[OH]2.4MgCO3.5H_2O$) 0.97%, potassium iodide (KI) 0.02%, sodium sulfate (Na_2SO_4) 0.07%, sodium chloride (NaCl) 98.83%.

VEE VO

Manufacturer.—Mayflower Food Products, Inc., New York.

Description.—Mixture of cane sugar, breakfast cocoa, malted milk, dried egg yolk (1 per cent), whole milk powder (0.5 per cent), dried malt (0.5 per cent) and flavored with salt and vanillin. The same as Vee Vo of the Titman Food Products, Inc., New York (THE JOURNAL, Sept. 14, 1935).

This product originally was manufactured by the Titman Food Products, Inc., and was accepted by the Council on Foods. Later it was removed from the market. The ownership of the Titman Food Products Company recently has reverted to the Mayflower Food Products, Inc. Vee Vo has been reinstated among the accepted foods of the Council.

PARKE, DAVIS & COMPANY'S EXTRACT VANILLA SPECIAL

Manufacturer.—Parke, Davis & Company, Detroit.

Description.—Vanilla extract containing water, alcohol, sugar and extractive matter of Bourbon and Tahiti vanilla beans.

Manufacture.—A blend of Bourbon and Tahiti vanilla beans, commercially dried and cured, is cut into small pieces, fully extracted by maceration and percolation with 50 per cent alcohol, after which the percolate is adjusted to proper volume by the addition of sugar and water.

Analysis (submitted by manufacturer).—Water, by weight, 38.8%; alcohol, by weight, 30%; total solids 31.2 Gm. per 100 cc.; ash 0.3 Gm. per 100 cc.; sucrose 28.0 Gm. per 100 cc.; vanillin 0.18-0.19 per 100 cc.; lead number (Winton) 0.35; specific gravity (approximate) 1.08.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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SATURDAY, MARCH 5, 1938

VIRUS INFECTIONS

Knowledge of viruses and virus diseases has progressed so rapidly that reviews are out of date almost as soon as published. The clinical lecture of Thomas M. Rivers[1] at the Kansas City session of the American Medical Association now needs to be supplemented. Van Rooyen and Rhodes[2] have recently reviewed the subject. Present investigations, they say, have tended to show that the so-called filtrable and ultramicroscopic viruses represent a range of living agents that differ from the bacteria only by virtue of their minute size and their inability to multiply in cell-free mediums. This view cannot be considered final, however, since Laidlaw and Elford in 1936 isolated from sewage a virus which was successfully cultivated in artificial mediums. Furthermore the living nature of viruses has been challenged by the work of Stanley and others, who isolated from plants affected by tobacco mosaic a crystalline protein which was capable of reproducing the disease when inoculated into other plants.

Certain viruses will grow readily in the presence of living cells, provided they are suitably supported, nourished and warmed. The use of the chick embryo for virus research, described by Burnet[3] in 1936, has proved an invaluable aid to investigations. It has enabled the production of vaccinial material for human vaccination from the egg which is absolutely sterile and which has the same biologic properties as lymph produced from the calf.

The serum of an individual who has passed through an attack of virus disease will show specific neutralizing and other antibodies during convalescence. During this period the previously infected person is protected from further invasion; in fact, at one time it was considered that resistance to a second attack was an essential criterion of this group of infections; but this generalization is no longer possible. The therapeutic action of convalescent serums of measles is well known; but whereas it is of value when given early, it appears to be relatively useless when administered during the late stages of the disease.

Direct contact of the skin or mucous membrane is a common route of transmission of virus diseases, examples of which are variola, vaccinia, herpes, molluscum contagiosum, warts and venereal lymphogranuloma. In other diseases, such as measles, mumps, influenza and psittacosis, droplet infection may be the route of transmission. Many virus diseases of man are communicated through animal, insect or arthropod vectors. A number of naturally occurring virus diseases of animals have been shown to be communicable to man, such as rabies, Rift Valley fever, louping-ill and foot-and-mouth disease. The incubation period between the entrance of the virus into the host and the development of signs and symptoms is a characteristic feature of virus disease, but the interval may vary greatly in duration. An extreme example is cited by van Rooyen and Rhodes, who report a case of rabies in a veterinarian six months after being licked by a rabid dog. Having gained access to the tissues of the host, a virus either may cause a generalized infection throughout the body or may exert a selective affinity for one of its tissues. The mode and rate of virus excretion is of interest to public health authorities; it is already apparent that in many instances viruses may remain for considerable periods in the tissues, and individuals harboring them may act as carriers.

Acquired immunity to certain virus infections may be obtained by immunizing either with living attenuated virus or with dead virus suspensions. The present status of attempted immunization in influenza has been referred to in a previous editorial.[4] The method of immunization in yellow fever, described in 1937, consisting of injecting immune human yellow fever serum, followed later by a small dose of live neurotropic virus, is earnest of further progress in this direction.

Another interesting review of the immunologic reactions of viruses has been published recently by Burnet and his co-workers.[5] The majority of the workers in this field, these authors say, have held that virus neutralization reactions are manifestations of virus-antibody union. Summarizing their interpretation of this reaction, they state that a virus inactivation by immune serum results primarily from union of antibody to the virus surface. This union is reversible and takes place at a rate and reaches an equilibrium determined by the ordinary laws of reversible chemical unions. The union of antibody has no intrinsic inactivating effect on the virus but the inactivation is the result of the interaction between susceptible cell and antibody-coated virus particle. In practice, however, the experi-

1. Rivers, T. M.: Recent Advances in the Study of Viruses and Viral Diseases, J. A. M. A. **107**: 206 (July 18) 1936.
2. van Rooyen, C. E., and Rhodes, A. J.: A Survey of Virus Infections, Glasgow M. J. **11**: 1 (Jan.) 1938.
3. Burnet, F. M.: The Use of the Developing Egg in Virus Research, Medical Research Council, Special Report Series No. 220, 1936.
4. Progress in Influenza, editorial, J. A. M. A. **109**: 1202 (Oct. 9) 1937.
5. Burnet, F. M.; Keogh, E. V., and Lush, Dora: The Immunological Reactions of the Filtrable Viruses, Australian J. Exper. Biol. & M. Sc. **15**: 231 (Sept.) 1937.

mental results obtained with any given virus will deviate from theoretical values due to variation in range of virus population, time required to reach equilibrium, lag between time of inoculation and initiation of a demonstrable lesion, secondary reactions, and mixtures of virus with relatively large amounts of serum.

PROTEINS OF FIRST IMPORTANCE

The extraordinary ease with which chemical transformations proceed at physiologically normal temperatures in the organism, in contrast to the difficulty involved in conducting similar reactions in the laboratory, is attributable to the existence of catalytically active agents. Although some of the changes can be directly related to the operation of physical laws, certainly the majority of the many hundreds of known bodily processes owe their amazing specificity and velocity of reaction to biocatalysts. Obviously, therefore, a clearer concept of the mechanism of the fundamental processes of metabolism which occur in every living cell and on which the life of these structural units depends can be gained from a better understanding of the substances which influence the course of these primary chemical mechanisms. Ever since investigators have concerned themselves with the chemistry of vital processes, the proteins have exercised a peculiar fascination. Not only are the proteins the fundamental building material of the cell protoplasm, but the particular group of substances which catalyze life processes are also protein in nature. Although we still lack an exact knowledge of the structure of a single protein molecule, the persistent efforts of investigators and the continued introduction of newer methods, particularly within the last decade, have opened unsuspected horizons to the vision of the investigator of proteins. Results have been secured which promise to transcend the boundaries between the living and the lifeless and which have contributed enormously to the fund of information regarding both the normal and the pathologic processes of organisms. Of particular importance in this field is the work of Northrop, Chandler medalist. His lecture delivered on the occasion of the award of the medal [1] presents an excellent summary of recent investigations of biocatalysts as proteins.

The chemical nature of the enzymes, the chief group of biocatalytically active substances, was quite unknown until a few years ago. The first enzyme to be isolated in crystalline form was urease, and this substance was found to be a protein. In the last decade, pepsin, trypsin, chymotrypsin, carboxypeptidase, amylase, catalase and several other enzymes have been obtained in crystalline form, and each has been shown to be a protein. It appears therefore that the characteristic and fundamental chemical reactions which occur in living cells are caused by the presence of minute amounts of certain peculiar proteins. Thus the chemical nature of enzymes is now well established and considerable information is available regarding their mode of action. One of the most interesting phases of the study of enzymes has been the effort to determine the portion of the protein molecule responsible for the catalytic activity. In some instances it has been demonstrated that this activity can be attributed to the presence of a group which is conjugated with the protein molecule, the so-called prosthetic group. This is true, for example, in the case of the yellow respiratory ferment studied by Warburg. In the case of biocatalysts in whose structures no prosthetic group or other readily detected structure has been found to which to assign the catalytic action, it appears that the activity depends on some peculiar arrangements of the amino acid components of the protein molecule. This is probably true, for example, of pepsin. Although efforts to identify the particular arrangement or active groupings in such molecules have been unsuccessful, it has been possible to prepare several proteins which are closely related to the active enzymes but which are themselves inactive. Furthermore, careful studies of the differences between such inactive proteins and the active enzymes have demonstrated that comparatively slight changes in an inactive protein may result in the formation of the active enzyme. Under these conditions the reaction is autocatalytic; i. e., some enzymes possess the power to form themselves from inert proteins.

The phenomenon of autocatalytic production of these biocatalysts from inactive protein may be translated to the field of virus proteins, in which rapid progress has recently been made. Crystalline proteins have been isolated which, when inoculated into healthy tissue, produce pathologic growths characterized by an increased production of the catalytically active protein or virus molecule. A synthesis of new virus protein is initiated and continues to take place at the expense of the normal cell tissue. Here indeed is an astounding observation: the ability of an inert, lifeless, crystalline organic molecule to initiate what is probably an autocatalytic production of itself. Similar results have been reported by Northrop for bacteriophage. A practically homogeneous protein of huge molecular weight (approximately 200,000,000) has been isolated from lysed staphylococci culture. This protein possesses the properties of bacteriophage, being capable of increasing when inoculated into a growing culture of staphylococci and eventually causing complete dissolution of the bacteria. This protein also, in common with some of the crystalline virus proteins, possesses the property of increasing in the presence of living cells. It remains to be definitely established whether these biocatalysts produce themselves autocatalytically from a precursor present in normal cells or whether they initiate a synthesis of themselves from simpler compounds. It has been established that the biocatalysts which have been studied are proteins and that investigation of these proteins has served to eliminate certain distinctions between living

1. Northrop, J. H.: Science **86**: 479 (Nov. 26) 1937.

and lifeless. As crystalline, organic compounds, these materials are lifeless; as substances which have the property of increasing in the presence of living cells, they assume a property characteristic of living things. More and more it appears that the value of adequate knowledge of the chemistry and the metabolism of proteins is necessary to an understanding of normal and pathologic processes. Truly, this group of substances richly deserves its name, proteins, which means "of first importance."

EPILEPSY

The term "epilepsy," derived from the Greek word meaning "a seizure," connotes only the clinical manifestation. Now, after a thousand years, the acquisition of information on the underlying pathologic physiology permits an entirely new concept of this syndrome. Among the investigations responsible for this clarification, those by Gibbs and his colleagues have taken an important place. Their most recent report,[1] dealing with the use of the electro-encephalogram, further corroborates the view that an attack of epilepsy is associated with the development of abnormal rhythms in the cerebral cortex and is hence a paroxysmal cerebral dysrhythmia.

Seven new facts about epilepsy seem to have been gained in the past two and one-half years by means of the electro-encephalogram. An epileptic seizure is accompanied by disturbances in the normal electrical activity of the brain or, more exactly, a clinically observed seizure is merely the outward manifestation of a disordered rhythm of brain potentials. Some patients observed during seizures, however, do not show abnormality of rhythm. The explanation, the investigators believe, is that the condition of the involved portion of the brain is not being recorded. Although this interpretation seems plausible, it lacks adequate substantiation. The three main clinical types of seizure—petit mal, grand mal and psychic variant—have distinct recognizable cerebral rhythms. The abnormal rhythms are clearly the causes of those symptoms (loss of consciousness and abnormal movements of the muscles) which constitute the seizures of epilepsy. The more fundamental basis of the disorder, however, is not the abnormal rhythm but rather a defective control of the rhythm. Furthermore, the electro-encephalogram often reveals abnormalities of electrical activity which are not at the time evident by subjective or objective clinical manifestations. The picture may be of the same pattern as that found during a clinical seizure but diminished in duration and voltage. At times grand mal and psychomotor attacks may be predicted by observation of the electro-encephalogram before any clinical sign is manifest.

When the electrodes are placed at different points on the scalp, it is possible to speak with assurance only of what takes place over the various readily accessible areas of the cortex. Abnormal rhythms commonly appear first in the frontal area but may arise first in the parietal or occipital areas. Finally, when abnormalities of rhythm are frequent, a few hours' observation is sufficient to determine whether the condition is improved or made worse by a given drug or treatment. Petit mal rhythms may be precipitated by a short period of overventilation and may dramatically disappear while the patient is breathing air containing from 3 to 7 per cent of carbon dioxide. Abnormal rhythms are also increased by insulin and decreased by dextrose. Sedative drugs have varying effects, depending on the type of abnormal rhythm.

Although this method of investigation is less than three years old, it has already contributed enormously to the understanding of the pathologic physiology of epilepsy and the differentiation of the various types by other than clinical criteria. It warrants the hope that methods of treatment can be improved by objectively observable means and portends a greater degree of individualized effective therapy.

1. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **60**: 24 (Dec.) 1937.

Current Comment

CANCER IN EARLY LIFE

Elsewhere in this issue (page 703) appears a study by Hall and Bagby on the frequency of cancer during the first three decades of life. Since 1908 there have been 134 patients at the Barnard Free Skin and Cancer Hospital between the ages of 8½ and 31 in whom a diagnosis of cancer was confirmed by microscopic examination. The youngest patient in the series was 8½ years old; the youngest with carcinoma of the lip, 19; of the breast, 22 (two patients); of the ovary, 15, and of the cervix, 20 years. This record strongly affirms the fact that cancer can and does occur in young persons in practically all anatomic locations. As in cancer of later life, the prognosis is intimately dependent on early diagnosis and satisfactory treatment.

PHYSICAL AND EMOTIONAL PERIODICITY IN WOMEN

The occurrence of a female reproductive cycle indicates a hormone periodicity that is well recognized. Nevertheless, previous to the study of McCance and his co-workers [1] there seems to have been no sustained attempt to obtain systematic records of the psychology and subjective and physical changes that accompany the cycle. Using a modification of the questionnaire-diary method, they obtained the day-to-day records over a period of from four to six months of the physical changes and subjective phenomena of 167 normal women. The data submitted covered 780 complete menstrual cycles and in addition data from a smaller group on physical changes only. The analysis revealed

1. McCance, R. A.; Luff, M. C., and Widdowson, E. E.: Physical and Emotional Periodicity in Women, J. Hyg. **37**: 571 (Oct.) 1937.

an average length of menstrual cycle of 27.8 days, with a standard deviation of 3.4 days. This however was an average, and individual cycles were often characteristically short or long, regular or irregular. No woman menstruated with complete regularity (measured in days) over a period of six months. An interesting feature of the study was the notation that 23 per cent of the menstrual periods began between 7:30 and 9:30 a. m. and the average duration of flow was about 4.5 days. The periodicity for each of the subjective phenomena was averaged and recorded graphically. On this basis, fatigue showed a definite relation to the cycle, reaching an average peak at about the onset of the menstrual flow. Abdominal pain, pain in the back, mental depression and, to a lesser degree, irritability, tendency to cry, and effort required for intellectual work, were similarly related to the beginning of the cycle. The incidence of headache, however, reached a peak about the third day after the onset of the cycle rather than the first day. The graphic expression of the incidence of the breast changes showed an average incidence reaching a peak before the onset of the menstrual flow and falling rapidly thereafter. When obtained, the incidence of sexual feeling and sexual intercourse varied widely individually, but the mean showed an irregular peak in the early days of the postmenstrual period. While admittedly incomplete, and unsatisfactory in many respects, this study serves as a scientific attempt to secure accurate information of great practical importance.

DERMATOPHILIC POLIOMYELITIS

Although controversy still exists as to the method of spread of poliomyelitis, this doubt is not generally recognized by clinicians. It is apparently not generally known that monkeys can be infected with poliomyelitis virus through routes other than the nasal mucosa. For example, in 1935 Erber and Pettit [1] inoculated thirteen monkeys subcutaneously with a pooled virus. Twelve of their animals developed typical lethal poliomyelitis. In 1936 Levaditi and his co-workers [2] inoculated seventeen monkeys subcutaneously with a monovalent poliomyelitis vaccine. Ten of the inoculated monkeys developed lethal paralytic symptoms. Trask and Paul [3] of Yale University, Howitt [4] of the University of California and other American workers have reported similar cutaneous infectivities. In their latest studies of cutaneous infectivity Trask and Paul [5] of the Department of Pediatrics, Yale University School of Medicine, found that certain freshly isolated poliomyelitis viruses are highly infectious on intracutaneous injection but that this cutaneous infectivity is apparently lost after repeated passage through monkeys. Endermic injections with recently isolated 1934 Los Angeles virus, for example, or with freshly isolated 1937 Toronto virus, rarely fail to produce lethal paralysis. One of these dermatophilic strains (Los Angeles 1934) is apparently not infectious on intranasal instillation. The foregoing studies, and those of Toomey,[6] make it seem probable that clinicians have been too hasty in focusing their attention solely on the nasal mucosa as presumably the only portal of entry of this infectious disease. The Yale University pediatricians have rendered a distinct service in calling attention to other possibilities.

1. Erber, B., and Pettit, A.: Comp. rend. Soc. de biol. **117:** 1175, 1934.
2. Levaditi, C.; Kling, C., and Haber, P.: Bull. Acad. de méd. **115:** 431 (March 10) 1936.
3. Trask, J. D., and Paul, J. R.: J. Bact. **31:** 527 (May) 1936.
4. Howitt, B. F.: Science **85:** 268 (March 12) 1937.
5. Trask, J. D., and Paul, J. R.: Science **87:** 44 (Jan. 14) 1938.
6. Toomey, J. A.: Active and Passive Immunity and Portal of Entry in Poliomyelitis, J. A. M. A. **109:** 402 (Aug. 7) 1937.

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

CALIFORNIA

Plague Infection — According to *Public Health Reports,* plague infection had been proved, by animal inoculation and by cultures, in twenty-nine fleas from five beecheyi squirrels collected Nov. 3, 1937, in the Shaver Lake area, Fresno County.

Society News.—The program of the February 17 meeting of the Los Angeles County Medical Association was presented by the obstetric section with the following speakers: Drs. Sterling N. Pierce, "Accidents at Cesarean Sections"; William Benbow Thompson, "Failures of Induction of Labor"; Raymond D. McBurney and Philip A. Reynolds, "Care of Parturient Women Under Analgesia," and George H. Kress, county hospital problems.

Publications in Pharmacology.—It is announced that the *University of California Publications in Pharmacology* will make their appearance early in the spring. These studies will appear irregularly but will be consecutively paged to form volumes of about 500 pages. Each issue will contain reports of original pharmacologic studies from the university's laboratories together with occasional review and general articles relating to the science. The editors are Gordon A. Alles, Ph.D., Troy C. Daniels, Dr. Mayo H. Soley and Chauncey D. Leake, Ph.D. A sample copy of the first paper may be obtained without obligation by writing to the University of California Press, Berkeley. It is expected that a volume will be completed about every three years. The subscription price will be $5.

COLORADO

Society News.—Dr. Charles P. Stockdale, Tioga, discussed "The Handling of Impetigo in Rural Schools" before the Huerfano County Medical Society, January 13, and Dr. Abram F. Stanley, Walsenburg, "Rural Health Problem Under WPA Difficulties."——Dr. Gilbert E. Haggart, Boston, addressed a special meeting of the Medical Society of the City and County of Denver, January 26, under the auspices of the Rocky Mountain Orthopedic Club, on "Sciatica and Low Back Pain: Methods of Diagnosis and Treatment."

DELAWARE

Society News.—Dr. John M. Bergland, Baltimore, read a paper before the New Castle County Medical Society in Wilmington, January 14, entitled "The Attempt to Relieve the Pain of Labor." Dr. Fred H. Albee, New York, addressed the society recently on "Bone Reconstruction Surgery." Dr. Edward T. Crossan, Philadelphia, discussed "Acute Hematogenous Osteomyelitis" before the society in Wilmington February 15.

FLORIDA

First Tuberculosis Sanatorium in Florida. — The first state tuberculosis sanatorium in Florida was opened January 3 near Orlando. Dr. Jay Arthur Myers, Minneapolis, president of the National Tuberculosis Association, was the principal speaker. Others on the program included Drs. Edward Jelks, Jacksonville, president of the Florida Medical Association; Wilmoth H. Baker, Tallahassee, state Negro tuberculosis committee; Rev. E. C. Gillette, Jacksonville. The sanatorium is a three story brick and concrete structure and located on one of the highest points adjacent to Orlando. It overlooks a lake, and

is in the center of a 160 acre tract of land donated by the city of Orlando. The sanatorium, with equipment, powerhouse, sewage disposal plant, laundry and nurses' cottages, cost about $700,000. It was financed through a state appropriation and a loan-grant from the federal emergency administration of public works. The building has single rooms and two, four and six bed wards. It is equipped to accommodate 312 patients but will house more than 400 when the state tuberculosis board has funds to purchase additional equipment. Two operating rooms are located on the third floor as well as a laboratory

Florida's first tuberculosis sanatorium.

and x-ray department. One wing of the building is for 125 Negro patients, with the same facilities as those for white patients. Dr. Rollin D. Thompson, formerly medical director and superintendent of the Wisconsin State Tuberculosis Sanatorium, Statesan, Wis., is the head of the new institution.

INDIANA

Society News.—Dr. Lillian R. Smith, Lansing, Mich., among others, addressed the Tippecanoe County Medical Society in Lafayette March 8 on "Summer Round-Up Program for Children."——Dr. Michael L. Mason, Chicago, addressed the Northeastern Indiana Academy of Medicine in Kendallville February 24 on "Management of Injuries to the Hand."

Committee to Study Marriage Laws.—Governor M. Clifford Townsend recently appointed a special committee to study the Indiana marriage laws with a view to necessary revisions. The work will include a comparison of the laws of other states. Medical representatives on the committee include:

Dr. Herman M. Baker, Evansville, president, Indiana State Medical Association.
Dr. Harold J. Norton, Columbus.
Dr. Thurman B. Rice, Indianapolis, Indiana University School of Medicine.
Dr. Eldridge M. Shanklin, Hammond, editor of the state medical journal.
Dr. Floyd R. Nicholas Carter, South Bend, chairman, syphilis committee, state medical association.
Dr. Arthur F. Weyerbacher, Indianapolis.
Dr. Louis P. Harshman, Fort Wayne State School.
Miss Marie Winkler, R.N., Indianapolis, president, state nurses' association.
Dr. George E. Denny, superintendent, Muscatatuck Colony, Butlerville.
Senator Thomas Hendricks, Indianapolis, secretary, state medical association.

KANSAS

Federal Aid for Venereal Disease Control.—The Kansas State Board of Health has recently received a grant of $2,400 from the U. S. Public Health Service to finance graduate courses among the medical profession of the state in venereal disease, tuberculosis and cancer control. These programs, which are now being organized, will be sponsored jointly by the board of health and various committees of the Kansas Medical Society.

Society News.—Dr. Edgar Van Nuys Allen, Rochester, Minn., addressed the Shawnee County Medical Society February 7 in Topeka on hypertension.——At a meeting of the Sedgwick County Medical Society, January 18, Drs. James E. Chipps discussed "Medical Ethics," and Leslie E. Knapp and Alonzo P. Gearhart, "Fractures in the Growing Age." All are from Wichita. The society was addressed February 1 by Drs. Arthur L. Ashmore and Vincent L. Scott, Wichita, on "Treatment of Empyema" and "Convulsions in Infancy and Childhood" respectively.——Dr. Wirt A. Warren, Wichita, discussed "Treatment of Chronic Arthritis" before the Reno County Medical Society January 21.

LOUISIANA

Personal.—Dr. Isadore Brickman has been appointed superintendent of the State Colony and Training School, Alexandria; he had been acting superintendent since the resignation of Dr. Rutledge C. Tompkins on account of ill health.

Society News.—A symposium on bronchogenic carcinoma constituted the program of the Orleans Parish Medical Society, New Orleans, February 14; the speakers were Drs. Stanford Chaille Jamison, Ernest C. Samuel, Eleazar R. Bowie and Antonio Mayoral, Harold L. Kearney, Bela Halpert and Edward William Alton Ochsner.——Dr. William H. Seemann, New Orleans, was recently reelected president of the Tuberculosis and Public Health Association of Louisiana.

MAINE

Hospital News.—The Bingham Associates Fund sponsored a clinic at the Rumford Community Hospital, January 12; Dr. Samuel H. Proger, Boston, delivered a lecture on obesity.

Society News.—Dr. Joelle C. Hiebert, Lewiston, was chosen president of the Maine Hospital Association at its recent annual meeting; Dr. Stephen S. Brown, Portland, vice president, and Margaret A. Hebert, R.N., Gardiner, secretary.

MARYLAND

Public Lecture on Vitamin Deficiency.—Karl E. Mason, Ph.D., associate professor of anatomy, Vanderbilt University School of Medicine, Nashville, Tenn., delivered a public lecture in the De Lamar series in hygiene at Johns Hopkins University School of Hygiene and Public Health, February 15; his subject was "Vitamin Deficiency as Related to Reproductive Structure and Function."

Graduate Course in Medical History.—For the first time a graduate week in medical history will be held at the Institute of the History of Medicine, Johns Hopkins University School of Medicine, Baltimore, April 18-23. The program has been arranged so that every morning one lecture on some basic subject will be given by Dr. Henry E. Sigerist, director of the institute, and members of his staff. Demonstrations will be held and the lectures will be followed by a general discussion. The afternoons will be devoted to round table seminars.

MASSACHUSETTS

Hospital News.—The New England Hospital for Women and Children, Boston, commemorated its seventy-fifth anniversary in December.

Personal.—Dr. Mary R. Lakeman, Boston, has been appointed northeastern regional director for the Women's Field Army of the American Society for the Control of Cancer. Dr. Lakeman retired Dec. 1, 1937, from the Massachusetts Department of Public Health, with which she had been associated for twenty years in child and adult hygiene work.

Society News.—The New England Pathological Society was addressed February 17, among others, by Drs. Leo Alexander, Tsung-hwa Suh and Tracy J. Putnam on "The Vascular Pattern in Various Studies with the Benzidine Stain." All are of Boston.——The Worcester District Medical Society was addressed February 9 by Drs. Walter E. Barton and Louis H. Cohen, both of Worcester, on "Advances in the Therapeutics of the Psychoses" and "Use of Metrazol in Schizophrenia" respectively.

MICHIGAN

Personal.—Dr. Charles H. P. G. Benning, Peoria, Ill., has been appointed district health officer of Royal Oak, a position he held prior to his appointment as school physician in Peoria.——Dr. Don W. Gudakunst, recently appointed health commissioner of Michigan, was guest of honor at a dinner January 19 given by members of the Detroit Department of Health.

The Dr. Max Ballin Memorial Lectures.—The fifth series of the Dr. Max Ballin Memorial Lectures, sponsored by the North End Clinic, Detroit, as a graduate teaching endeavor, will be held at the Detroit Institute of Art. The series this year will be devoted to gynecology with the following speakers:

Dr. George A. Kamperman, Detroit, Recent Trends in Gynecologic Practice, March 9.
Dr. Irving F. Stein, Chicago, Sterility, March 16.
Dr. Norman F. Miller, Ann Arbor, Mich., Cancer of the Female Generative Tract, March 23.
Dr. Charles Mazer, Philadelphia, Endocrinology in Gynecology, March 30.

Society News.—Dr. Louis Fernald Foster, Bay City, secretary, state medical society, addressed the St. Clair county medical and bar associations in Port Huron January 18 on "Professional Cooperation and Advancement."——Dr. Horton R. Casparis, Nashville, Tenn., discussed mental health before the Wayne County Medical Society and the Detroit Pediatric Society at a joint meeting February 21.——The Maimonides Medical Society, Detroit, was addressed February 8 by Dr. Bernard Fantus, Chicago, on "Recent Advances in Therapeutics."——At a meeting of the Genesee County Medical Society in Flint February 16 Dr. Norman E. Clarke, Detroit,

spoke on "Thyroidectomy in Treatment of Heart Disease."—— The Calhoun County Medical Society was addressed in Battle Creek February 1 by Dr. Udo J. Wile, Ann Arbor, on diagnosis and treatment of syphilis.——Dr. Richard H. Freyberg, Ann Arbor, discussed "An Appraisal of Our Knowledge Regarding the Etiology of Rheumatoid Arthritis" before the Muskegon County Medical Society in Muskegon, February 18.

Committees Named to Coordinate Health Activities.—The creation of a committee representing various health and medical agencies and an interdepartmental committee within the state administration for the coordination of public health activities in Michigan was recently announced by Governor Murphy. The first committee's function will be to arouse the interest of communities in their health problems, secure the cooperation of professional and educational groups, especially the medical and dental professions, and bring about a close working relationship between official and nonofficial agencies. It will be made up of the following persons:

Dr. Don W. Gudakunst, state health commissioner.
Dr. John Sundwall, professor of hygiene and public health and director, division of hygiene and public health, University of Michigan Medical School, Ann Arbor.
Dr. Bernard W. Carey, medical director, Children's Fund of Michigan, Detroit.
Dr. Matthew R. Kinde, medical director, W. K. Kellogg Foundation, Battle Creek.
Dr. Ledru O. Geib, chairman of the preventive medicine committee of the Michigan State Medical Society, Detroit.
P. C. Lowery, D.D.S., Detroit.

MISSISSIPPI

Society News.—The Central Medical Society was addressed in Jackson January 4, among others, by Drs. Albert G. Ward and Isaac C. Huggins, both of Jackson, on "Management of Patients Presenting Cardiac Symptoms" and "Cancer of the Rectum" respectively.—— A recent meeting of the Winona District Medical Society in Winona was addressed by Drs. William C. Chaney, Memphis, Tenn., on "Practical Approach to the Problem of Food Idiosyncrasy"; Thomas H. Blake, Jackson, "Fracture About the Hip," and Robert E. Wilson, Greenville, "Obscure Fever of Infants and Children."

MISSOURI

Annual Clinical Conference of Radiologists. — The annual clinical conference of midwestern radiologists was held at the Muehlebach Hotel, Kansas City, February 11. The speakers included:

Dr. Joseph E. Welker, Clinical Differentiation of Coronary Disease and Upper Abdominal Pathology.
Dr. Edward H. Skinner, Evolution of Radiation Therapy for Carcinoma of the Cervix.
Dr. Cecil G. Leitch, Clinical Analysis of Sudden Death from Cardiac Disease.
Dr. Fred E. Angle, Clinical and Roentgenological Data in Brucellosis.
Dr. Robert Lee Hoffmann, Clinical and Roentgenologic Findings in Trauma of the Genito-Urinary Tract.
Dr. Ferdinand C. Helwig, Ovarian Influence in Cancer.

Other speakers participating in a symposium Friday afternoon included Henry C. Tracy, Ph.D., Lawrence, Kan., on "Anatomy of the Breast" and Dr. Nymphus Frederick Hicken, Omaha, "The Visualization and Diagnosis of Breast Lesions by Means of Contrast Roentgenograms."

NEW YORK

Warning Against Premature Use of Rabbit Serum for Pneumonia.—The advisory committee on pneumonia control of the New York State Department of Health recently adopted a resolution warning against premature general use of rabbit serum in the treatment of pneumonia. In a statement in which the resolution was made public Dr. Edward S. Godfrey Jr., state health commissioner, referred to recent articles in lay publications and radio announcements which he declared have by implication promoted impressions that the new serum will shortly make available effective treatment for all types of pneumonia. In its resolution the committee stated that in certain cases its use is justified, but otherwise application of the rabbit serum should be limited to clinical trial in selected hospitals where careful observations can be made, until the value, safety and limitations of the method can be more accurately defined. Dr. Russell L. Cecil, New York, is chairman of the advisory committee.

New York City

Personal. — Dr. Charles E. Remy, superintendent of the Minneapolis General Hospital for several years, has been appointed superintendent of the Knickerbocker Hospital, to succeed Mr. Walter Mezger, who resigned to become associate director of Michael Reese Hospital, Chicago.

Assistant Dean Appointed.—Dr. John Hugh Mulholland, assistant clinical professor of surgery at New York University College of Medicine, has been appointed assistant dean. Dr. Mulholland graduated from the college in 1925. The university council also announced the promotion of Dr. John A. Lawler Jr. to be assistant clinical professor of surgery.

Funds for Research on Chronic Disease.—An appropriation of $66,000 has been made available by the Rockefeller Foundation to the department of hospitals for support of research on chronic diseases at the hospital now under construction on Welfare Island. Research on chronic diseases is now in progress in temporary quarters at Metropolitan Hospital and will be transferred to the new hospital as soon as possible. The subjects now being studied include rheumatoid arthritis, the role of nutrition in chronic disease, the role of cholesterol metabolism in arteriosclerosis, circulatory and respiratory functions in pulmonary emphysema, bacteriologic and immunologic factors in acute and chronic glomerulonephritis and various factors in hypertension.

Gibbs Medal Awarded for Vitamin Research.—Robert R. Williams, Sc.D., chemical director of the Bell Telephone Laboratories, will receive the Willard Gibbs Medal awarded by the Chicago Section of the American Chemical Society, it is announced. The medal will be presented at a meeting in Chicago April 29, honoring Dr. Williams "for outstanding work in connection with the study and isolation of the beriberi vitamin." Dr. Williams was born in India of American parents in 1886 and was educated at the University of Chicago. He spent several years as chemist for the Bureau of Science in Manila, P. I., returning to the United States in 1915. He was a chemist in the government service in Washington until 1919, when he joined the Western Electric Company. In 1925 he was made chemical director of the telephone company laboratories. He is also a research associate at Teachers College, Columbia University, and the Carnegie Institution of Washington.

Society News.—Drs. Joseph H. Globus and James F. Bing addressed the New York Endocrinological Society, January 26, on "The Pineal Body: Notes on Its Embryogenesis and Tumor Formation and Its Relation to Pubitas Praecox."——A symposium on carcinoma of the breast was presented at a meeting of the Bronx County Medical Society, January 19, by Drs. Milton R. Bookman, Frank E. Adair and Herbert C. Chase.—— At the annual dinner of the Faculty Association of the New York Post-Graduate Medical School and Hospital, January 29, Drs. Walter T. Dannreuther, George M. MacKee, Clarence G. Bandler and Willard C. Rappleye discussed graduate medical education and the control of specialization.——Dr. Howard W. Haggard, New Haven, Conn., addressed the New York Academy of Medicine, February 3, on "The Conception of Cancer Before and After Johannes Müller." —— Drs. Arthur M. Shipley, Baltimore, and William H. Stewart addressed the New York chapter of the National Society for the Advancement of Gastro-Enterology, January 31, on "Some Unusual Cases of Appendicitis" and "Cineroentgenographic Studies of the Gastro-Intestinal Tract" respectively.

NORTH DAKOTA

Personal.—Dr. John R. Pence, Minot, has recently been appointed health officer of Ward County.——Dr. Charles Albert Arneson, Bismarck, has been named health officer of the city. ——Dr. Frederick Charles Lorenzen, Elgin, has been named superintendent of the North Dakota State Hospital, Jamestown.——Dr. Frank W. Deason, Grafton, recently succeeded Dr. James Prentiss Aylen, Grafton, as superintendent of the North Dakota State School for the Feebleminded at Grafton.

OREGON

Alumni Meeting. — The annual graduate session of the Alumni Association of the University of Oregon Medical School will be held in Portland March 7-9. Dr. Charles P. L. Mathe, San Francisco, will be the guest speaker.

Society News.—Dr. John H. Besson addressed the Multnomah County Medical Society, Portland, February 16, on "Bilateral Uretero-Intestinal Implantation, with Cystectomy and Hysterectomy at One Operation" and Drs. Thomas D. Robertson and James Marr Bisaillon, on "Lobar Pneumonia: Some Newer Aspects, Including Typing."——Dr. Goodrich C. Schauffler, Portland, addressed the Central Willamette Medical Society, Corvallis, January 6, on "Occiput Posterior and Obstetric Emergency."

PENNSYLVANIA

New State Sanatorium Started. — Ground was broken February 14 for a new state sanatorium for tuberculosis near Butler in Butler County. The new hospital will be built to accommodate 500 patients, with a special wing for children. It will have twelve units, including the service plants, dormitories for employees and nurses' home. It is estimated that the project will cost about $2,645,000 and will be finished by May 1939.

Graduate Program at Geisinger Hospital.—The second graduate seminar of the year was presented at Geisinger Memorial Hospital, Danville, February 4, under the auspices of the Montour County Medical Society. In the morning Dr. Harold L. Foss conducted an operative clinic and the following program was presented later:

Dr. Roy D. McClure, Detroit, Treatment of Burns.
Dr. Wendell J. Stainsby, recently of New York, now of Danville, Chronic Arthritis.
Dr. Edward L. Bauer, Philadelphia, Rheumatic Infections.
Dr. Clyde M. Spangler, Philadelphia, Toxemias of Pregnancy.
Dr. Edward F. Roberts, New York, Pneumonia and Its Treatment with Serums.

Philadelphia

Medical College News. — Dr. Maurice E. Binet, Vichy, France, gave a lecture February 15, at the Hahnemann Medical College and Hospital of Philadelphia, on "Hepatic Insufficiency in the Course of Chronic Colitis."——Jean Broadhurst, Ph.D., New York, gave an address at the Woman's Medical College of Pennsylvania February 18 on "Virus Inclusion Bodies in Measles and Scarlet Fever."

New Dean of Pharmacy College.—Ivor Griffith, Sc.D., assistant dean of pharmacy and professor of theory and practice of pharmacy at the Philadelphia College of Pharmacy and Science, has been appointed dean of the college to succeed the late Charles H. LaWall. Dr. Griffith, born in Wales, graduated from the Philadelphia college in 1912 and has been associated with his alma mater in various capacities for many years. He has been editor of the *American Journal of Pharmacy*, published by the college, since 1921.

Faculty Changes at Jefferson. — Dr. Karl Kornblum, assistant professor of radiology, University of Pennsylvania Graduate School of Medicine, has been appointed professor of roentgenology at Jefferson Medical College. Dr. Kornblum graduated from the University of Pennsylvania School of Medicine in 1919. The following promotions in the Jefferson faculty were announced:

Dr. Thaddeus L. Montgomery, to be clinical professor of obstetrics.
Dr. Alexander Spencer Kaufman, associate professor of otology.
Dr. Arthur J. Wagers, assistant professor of laryngology.
Dr. Austin T. Smith, assistant professor of laryngology.
Dr. William P. Hearn, assistant professor of surgery.
Andrew J. Ramsay, Ph.D., assistant professor of histology and embryology.

Convicted in Charity Racket—Freed on Appeal.—Two of six men who were convicted several months ago as conspirators in a fake hospital charity drive were freed in superior court January 27, according to newspaper reports. The men were Thomas J. Goldberg, superintendent of the "Naturopathic Hospital," for which the alleged drive was conducted, and Harry S. Nurock, secretary of the Pennsylvania Society of Naturopaths (THE JOURNAL, Oct. 2, 1937, p. 1133). Judge Chester H. Rhodes said that evidence was not sufficient to show that Goldberg and Nurock were fully aware of the nature of the racket. It was said that a group of promoters proposed a dance for the benefit of the "hospital" and sold tickets by telephone. Salesmen impersonated physicians and stated that the money was to be used for victims of infantile paralysis. It was pointed out in the trial that the "Naturopathic Hospital" had no beds for patients but did have electrical and what appeared to be surgical equipment. The two men had been sentenced to two years in jail.

Pittsburgh

Society News. — The program of the Allegheny County Medical Society, February 15, presented the following speakers: Drs. Harvey Bartle, Philadelphia, on "Industrial Medicine"; James A. Cowan Jr., "The Technic of the Formation of the Tubed Flap and Its Utilization"; Howard G. Schleiter and Arthur B. Thomas, "Syphilis and the Circulatory Apparatus," and Robert C. Grauer, "Clinical Counterparts of Experimental Breast Tumors."——Dr. William J. Engel, Cleveland, addressed the Pittsburgh Urological Association, February 14, on "Management of Papillary Tumors of the Bladder."——A panel discussion of health problems of school children made up the program of the Pittsburgh Pediatric Society February 11; the speakers were Drs. Theodore O. Elterich, Harry B. Burns, Henry J. Benz, Russell R. Jones, John Watson Harmeier and Henry T. Price, and Mr. J. F. Guy, associate superintendent of the Pittsburgh public schools.

SOUTH CAROLINA

District Meeting.—A meeting of the Second District Medical Society was held at Batesburg, February 17, with the following speakers: Drs. James C. McLeod, Florence, on "Traumatic Abdominal Injury"; Richard B. Josey, Columbia, "Appetite in Children" and Herbert M. Smith, Columbia, "The Physician and the State Board of Health." Dr. Leonidas M. Stokes, Walterboro, president of the South Carolina Medical Association, also made an address.

Cancer Symposium.—The Tri-County Hospital at Orangeburg opened a cancer service with a symposium at which Drs. Ira I. Kaplan, New York, and Kenneth M. Lynch, Charleston, were the guests January 17. Both speakers addressed a public meeting, and a clinic was held in the hospital. Following a banquet at the Eutaw Hotel, Dr. Kaplan spoke on treatment of cancer by a combination of surgery, x-rays and radium and Dr. Lynch on pathogenesis of cancer.

Society News. — Dr. Chevalier L. Jackson, Philadelphia, addressed the Columbia Medical Society of Richmond County, Columbia, February 14, on "Foreign Body in the Air and Food Passages." Dr. Reginald Fitz, Boston, addressed the society January 10 on "Problems in Modern Diabetic Therapy" and Dr. Orlando B. Mayer, Columbia, on "Pancreatic Hemorrhage Followed by Fistula." —— Dr. Leonidas M. Stokes, Walterboro, president of the South Carolina Medical Association, addressed the Edisto Medical Society (Bamberg, Calhoun and Orangeburg counties) January 27 on "The Physician as a Citizen."

TEXAS

Tenth Dallas Clinical Conference. — The tenth annual spring clinical conference of the Dallas Southern Clinical Society will be held at the Hotel Adolphus, Dallas, March 14-17. There will be a general assembly each morning, followed after the first day by postgraduate courses. In the afternoons there will be clinics at the hotel and in the evenings different types of meetings. Guest speakers and their subjects at the general assemblies will be:

Dr. Nelse F. Ockerblad, Kansas City, Mo., Urology for the General Practitioner.
Dr. Jennings C. Litzenberg, Minneapolis, Treatment of Abortion.
Dr. Conrad Berens, New York, The Role of Physician and Surgeon in the Diagnosis and Treatment of Eye Disease.
Dr. Russell L. Haden, Cleveland, Treatment of Arthritis.
Dr. Charles H. Best, Toronto, The Prolongation of Insulin Action.
Dr. James C. White, Boston, Progress in Surgery of the Autonomic Nervous System.
Dr. Henry F. Helmholz, Rochester, Minn., Urinary Infections in Children.
Dr. Allen O. Whipple, New York, Treatment of Carcinoma of the Stomach.
Dr. Warren T. Vaughan, Richmond, Va., Modern Methods in the Study of Migraine.
Dr. Philip H. Kreuscher, Chicago, Fractures of the Hip and Other Major Joints.
Dr. Howard T. Karsner, Cleveland, Research on Hypertension.
Dr. George W. Mackenzie, Philadelphia, The Appearance and Behavior of the Normal Drumhead.

Monday evening Dr. Berens will speak on "Medical Economics"; a clinical-pathologic conference will be held Tuesday evening; symposiums on nutritional deficiencies, malignant disease and allergic rhinitis, Wednesday evening, and the annual clinic dinner Thursday evening. Other symposiums will be presented at the afternoon meetings on sulfanilamide, pancreatic disease and backache. In addition there will be luncheon conferences with the guest speakers each day.

WASHINGTON

Society News.—Drs. Donald V. Trueblood and Brien T. King, Seattle, addressed the Grays Harbor County Medical Society, Aberdeen, January 19, on "Tumors of the Neck and Parotid Gland" and "Congenital Sinuses and Anomalies of the Head and Neck" respectively.——Dr. James Marr Bisaillon, Portland, Ore., addressed the Walla Walla Valley Medical Society, Walla Walla, January 13, on "Differential Diagnosis of Chest Diseases."——At a meeting of the Yakima Valley Medical Society, Yakima, January 10, Dr. George F. Cooper, San Francisco, spoke on "Treatment of Pneumonia with Serum."——Drs. Frederick B. Exner and Frank L. Horsfall, Seattle, addressed the King County Medical Society, Seattle, February 21, on "Enlarged Thymus" and "Diverticulosis of the Colon" respectively.

WISCONSIN

William Snow Miller Lecture.—Dr. Herbert S. Gasser, director of the Rockefeller Institute for Medical Research, New York, will deliver the eleventh William Snow Miller Lecture, March 8, at the Service Memorial Institute Building, University of Wisconsin, Madison. The lecture is presented under the auspices of the Phi Beta Pi Medical Fraternity and the University of Wisconsin Medical Society. Dr. Gasser's topic will be "The History of Electrophysiology." Dr. Miller's eightieth birthday will occur March 29.

Conference of County Secretaries.—The annual conference of secretaries of county medical societies was held in Milwaukee January 9 with Dr. Samuel L. Henke, Eau Claire, as chairman. Among the subjects discussed were work of the special committees of the state society to study distribution of sickness care and hospital insurance, programs for county medical societies and malpractice insurance. Mr. J. George Crownhart, Madison, executive secretary of the state society, presented a report on medical care for the clients of the Farm Security Administration.

WYOMING

New State Board Ruling.—The Wyoming State Board of Medical Examiners recently adopted a resolution ruling that a physician who opens an office alone or associates himself with another physician before he obtains a license shall not be permitted to appear as an applicant for a license. It is considered that a man who thus attempts to practice has violated the medical practice act and is therefore not eligible to appear before the board as an applicant of good moral character.

PUERTO RICO

News of the School of Tropical Medicine.—George W. Bachman, Ph.D., director of the School of Tropical Medicine of the University of Puerto Rico in San Juan under the auspices of Columbia University, in his annual report stated that a study of the peasant diet has centered during the past year on the chemical composition, vitamin A content, ash analysis and protein adequacy of the island's forage crops. This research is carried on as a joint project with the agricultural experiment station. In cooperation with the Puerto Rico Reconstruction Administration a handbook on nutrition is being prepared. Health and socio-economic conditions in the island's sugar region are being studied by the department of bacteriology and the health division of the reconstruction administration. Dr. Bachman stressed the need of an endowment for the school.——Robert M. Yerkes, Ph.D., director of the laboratories of primate biology, Yale University, New Haven, Conn., lectured at the school of tropical medicine recently on "Morphine Addiction in the Chimpanzee." Dr. Donald S. Martin, Durham, N. C., is spending the winter working in the department of mycology and dermatology. H. D. Tate of the Bureau of Animal Industry, Washington, D. C., is studying the problem of tick eradication.

GENERAL

National Research Council Chairman.—Dr. Ross G. Harrison, Sterling professor of biology, Yale University School of Medicine, New Haven, Conn., has been elected chairman of the National Research Council. He succeeds Dr. Ludvig Hektoen, who has become executive director of the National Advisory Cancer Council of the U. S. Public Health Service.

Grants Available for Research in Child Neurology.—The council of Child Neurology Research, a fund set up in 1936 by the Friedsam Foundation, announces that applications for grants will be considered at the meetings to be held in April and October of each year. The purpose of the council is to encourage original research on definite problems coming within the scope of child neurology and allied fields. Applications must be in the hands of the director, Dr. Bernard Sachs, 116 West Fifty-Ninth Street, New York, before April 1 and September 15. The applicant must state distinctly the problem under investigation and the methods to be pursued.

Goiter Conference in Washington.—The third International Goiter Conference will be held in Washington, D. C., September 12-14. Physicians and others in the United States and other countries desirous of participating in the program are requested to submit titles at their earliest convenience. Subjects proposed for discussion are endemic goiter, cretinism and myxedema; the thyroid in relation to metabolism, nutrition and endocrine glands; and hyperthyroidism. The official language of the conference will be English, and interpreters will be furnished for papers read in other languages. For further information address officers of the American Association for the Study of Goiter or the chairman of the program committee. The secretary of the association is Dr. William Blair Mosser, Kane, Pa., and the program chairman is Dr. Allen Graham, 2020 East Ninety-Third Street, Cleveland.

Eye Swindler Attempts Suicide.—Ernest Mandell, one of a group of itinerant eye swindlers, pleaded guilty in federal court in Milwaukee January 12 to a charge of using the mails to defraud and was sentenced to serve thirty days in the house of correction. He was arrested at Nashville, Tenn., accused of defrauding a couple in Ripon, Wis., of $1,400 for "eye treatments" in 1933. Mandell attempted to commit suicide in jail, it is reported. A news item in THE JOURNAL, March 17, 1934, page 849, reported the arrest of an E. J. Mandell in Kentucky on a similar charge. For want of proof he was released with his companion at that time on condition that the $300 involved be refunded. Frank Faircloth, alias Frank Nelson, pleaded guilty to the same charge in Milwaukee, January 12, and was sentenced to four months in the house of correction. An indictment is pending against Mandell in Greene County, Pa., in connection with a swindle near Jefferson, and one against Faircloth in Mississippi. A roundup of these itinerant eye swindlers has been under way for some months by the U. S. Post Office Department.

Government Appeals from Decision Reversing Baker's Conviction.—The government has appealed to the supreme court in its case against Norman Baker, "cancer specialist," and E. B. Rood, charged with violating the federal communications act in connection with broadcasts from Station XENT, Nuevo Laredo, Mexico. A petition charged them with making mechanical reproductions of voices and music at Laredo, Texas, which were shipped to the radio station and broadcast. It stated that no permit had been obtained from the Federal Communications Commission. The government appealed from a decision of the fifth circuit court of appeals in December 1937 which reversed the conviction of the two men in the United States District Court for the Southern District of Texas, April 22, 1937. At that time Judge Thomas M. Kennerly sentenced Baker to spend four months in jail and pay a fine of $2,000 to the United States of America "for conspiracy to locate, maintain and use apparatus from which and whereby sound waves are and were converted into mechanical and physical reproductions of sound waves and to carry, transport and deliver to a radio broadcast station in a foreign country for the purpose of being broadcast from that station . . . and which said station . . . was so located geographically that its emissions . . . were received consistently in the United States, without first obtaining a permit from the Federal Communications Commission . . ." Rood received a sentence of four months in jail and a fine of $500 and a third defendant, Roy Richardson, one day in jail. The reversal of the conviction was obtained on the ground that section 325 B of the federal communications act of 1924 did not apply to the manufacture and shipment of phonograph records. Baker operated a radio station in Muscatine, Iowa, but in 1931 the federal commission refused to renew his license. He operates a hospital in Muscatine and recently opened the Baker Hospital in Eureka Springs, Ark., it is reported.

FOREIGN

International Neurological Congress.—The third International Neurological Congress will be held at Copenhagen, Denmark, in August 1939. Honorary presidents are Drs. Bernard Sachs, New York; Gordon M. Holmes, London, and Sir Charles S. Sherrington, Oxford. Dr. Henry Alsop Riley, New York, is among the vice presidents for the United States.

Sixteenth Physiological Congress.—The management of the sixteenth International Physiological Congress, to be held in Zurich, Switzerland, August 14-19, announces that April 1 is the final date for notification by persons who wish to appear on the program. It also states that each lecturer or demonstrator is requested to send a short summary of his communition by June 1 to be included in a volume issued to each member of the congress. There will be six main sections of the congress: general and comparative physiology; biophysics; biochemistry; applied physiology, especially nutrition of the people, work, sport and aviation physiology; experimental psychology, including the relation between psychical and somatic functions, and pharmacology. Further information may be obtained from Prof. E. Rothlin, 6, Sonnenweg, Basle, Switzerland.

Leprosy Conference in Cairo.—The fourth International Leprosy Conference will be held in Cairo, Egypt, March 21-31, under the auspices of the International Leprosy Association. The following delegation will represent the United States: Drs. Hermon E. Hasseltine, Carville, La., chairman; Victor G. Heiser, New York, president of the International Leprosy Association; Herbert W. Wade, Culion, P. I., medical director, Leonard Wood Memorial (American Leprosy Foundation) and editor of the *International Journal of Leprosy;* Jose Rodriguez of the Philippine Health Service, Manila, P. I.; James A. Doull, Cleveland; George M. Saunders, director of the epidemiological department, Leonard Wood Memorial; Mr. Perry Burgess, New York, president, Leonard Wood Memorial, and Mr. Emory Ross, general secretary, American Mission to Lepers. The group sailed on the S. S. *Exeter* March 1.

Deaths in Other Countries

Sir Frederic Truby King, former director of child welfare for New Zealand and founder of the Plunket Society for child and maternal welfare, died in Wellington February 9, aged 79.——**Sir James Crichton-Browne,** noted neurologist, Lord Chancellor's Visitor in Lunacy from 1875 to 1922, died at his home in Dumfries, Scotland, January 31, aged 97.——**Sir Thomas Stanton,** chief medical adviser to the government on tropical diseases, died in London January 25, aged 62.

CORRECTION

Graduate Medical Education: Michigan.—According to data made available at the Annual Congress on Medical Education and Licensure, February 15, there were 318, not 332, physicians enrolled for the intramural review courses at the University of Michigan Medical School and Wayne University College of Medicine and 1,497, not 1,235, practicing physicians of Michigan registered for graduate instruction in 1936-1937, as stated in the Organization Section of THE JOURNAL, February 5, page 73B.

Government Services

Promotions to Rear Admirals

Dr. Perceval S. Rossiter, surgeon general of the U. S. Navy, and Capt. Harold Wellington Smith, in charge of the Naval Medical School, Washington, D. C., have been promoted to the rank of rear admiral in the naval medical corps. Surgeon General Rossiter has held this rank on a temporary appointment since 1933. He is a native of Shepherdstown, W. Va., and graduated at the University of Maryland School of Medicine, Baltimore, in 1895. Captain Smith graduated at the Harvard University Medical School, Boston, in 1901.

Pathologists Wanted at National Institute

The U. S. Civil Service Commission announces open competitive examinations for positions at the National Institute of Health as medical pathologist (research) at $3,800 a year and associate medical pathologist (research) at $3,200. Applicants must have graduated from class A medical schools and served one year of internship. For the first position applicants must have been graduated since Dec. 31, 1916, and for the second since Dec. 31, 1929. Applicants for the position of medical pathologist must have had at least three years and those for the position of associate at least eighteen months of (*a*) graduate study in pathologic anatomy in an institution or department offering regular graduate courses in pathology or (*b*) graduate experience in pathologic anatomy and histology, or a combination of these requirements. Age limits are 53 and 45, respectively, for the two positions. Applications must be on file with the commission at Washington, D. C., not later than March 21 or March 24 if received from the following states: Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington and Wyoming. The necessary forms may be obtained from the board of civil service examiners at any first class postoffice, from the commission in Washington or from district offices of the commission in Atlanta, Boston, Chicago, Cincinnati, Denver, New Orleans, New York, Philadelphia, Seattle, St. Louis, St. Paul, San Francisco, Honolulu, Balboa Heights, Canal Zone, and San Juan, Puerto Rico.

Foreign Letters

LONDON

(From Our Regular Correspondent)

Feb. 5, 1938.

The Osteopaths and State Registration

At a meeting of the British Medical Association a discussion on "The Osteopath and State Registration" was opened by Dr. Charles Hill, deputy secretary of the association, who said that the modern osteopath had certainly diluted the doctrines of Still and that all seeking medical registration should satisfy the minimum requirements of the General Medical Council and then proceed in whatever direction they liked.

Dr. N. J. Macdonald, a physician and also a doctor of osteopathy, said that the British Osteopathic Association, whose members numbered between seventy and eighty, had formed a college committee which was trying to arrange for an establishment in London where students would be trained in medicine and surgery plus osteopathy. It could not succeed without the assistance of the medical profession, which he hoped would not be withheld. A voluntary register of osteopaths had also been set up. It comprised persons who practiced a particular form of treatment in much the same way as the holders of the diploma of medical radiology and electrology were registered. It could be made to serve as a liaison between the medical profession and the osteopaths.

Sir Ernest Graham Little, dermatologist and member of parliament, said that the chief reason for the failure of the osteopaths' bill was that the British osteopathic school proved thoroughly unsatisfactory on investigation. The American Medical Association placed the schools of osteopathy below its third or lowest class. Was the projected school in this country to be comparable to the medical schools? The difficulties were so great that they would do better to enlist the support of the existing medical schools, which he thought would be willing to institute osteopathic courses.

Sir Walter Langdon-Brown said that he was shocked to read in the evidence at the inquiry into the osteopaths' demand for registration that they contended that such diseases as typhoid could occur only where there was an "osteopathic lesion." At the same time he thought that in some respects osteopathy had made out its claim as a method of treatment. But as regards registration things should be left as they were. When a man passed the test of the General Medical Council he could adopt any theory he liked.

Dr. Hill said in reply that there seemed to be almost complete unanimity as to the undesirability of state registration of osteopaths. A prominent osteopath denied the germ theory of disease and opposed the administration of insulin in diabetes, saying that the "osteopathic lesion" was the almost exclusive cause of disease. The osteopath who had been taught from the beginning that a particular mode of treatment was indicated in many or most cases and that drugs were useless could not approach the problem of diagnosis with the necessary impartiality. The osteopath had something to contribute to general methods of treatment, but he should renounce Still.

The meeting was opposed to the registration of osteopaths, but the tolerance shown for methods with such an unscientific and even fantastic basis seems extraordinary. The important persons who took part in the discussion seem to have overlooked the possible explanation of the alleged good results from the treatment by suggestion or other extraneous circumstances. Tolerance is one of the great characteristics of the English, but, like other good qualities, it can be carried too far and here might be described as flabbiness.

"Nature" Barred in Germany

The German ministry of education has excluded the English scientific weekly *Nature* from general use in scientific libraries on the ground that it has contained attacks on German science and the government. Arrangements can still be made, however, for the secret use of the journal with restricted access. Commenting on this, *Nature* says that it welcomes the opportunity of recording worthy additions to science from any country or race "but should be false to the traditions of science if we failed to condemn any influence which would make scientific research subservient to political or theological domination."

Gas Masks Stored in Nitrogen

The government's stock of gas masks for the civilian population now amounts to 26,000,000 and they are being produced at the rate of 650,000 a week. More than 9,000,000 are at present stored in the London area. There is little doubt that the production is greater than that of any other country. To ensure that this great stock shall not deteriorate but remain fully effective, they are stored in special depots under careful conditions. The face piece is stored in nitrogen at a concentration of two atmospheres. For these reasons it is not possible to distribute the masks to the people at present. They are now stored in big regional depots, but it is contemplated that each local authority shall provide storage for those required in its area. It is essential that plans should be made for quick distribution of the masks in time of emergency. It is therefore contemplated that there should be storage depots holding about 30,000 masks each.

An Allergen Filter for Asthmatic Persons

At the Royal Society of Medicine, Dr. E. Fraenkel described a type of gas mask which he devised in collaboration with the engineers of a German manufacturer of gas masks, working in conjunction with a ventilating fan, for the use of persons who suffer from asthma. Thirty liters of air per minute can be drawn through the filter, but the quantity can be regulated. The filter is impermeable to pyridine, capronic acid, skatole, tobacco smoke, ammonia, chlorine and phosgene, and atomization with microbes such as B. coli and B. prodigiosus showed that it retained 97 per cent of them. Dr. Fraenkel recommended the use of the filter in certain trades and against climatic factors such as dust and pollens. But its chief value seems to be in treating asthmatic patients when ordinary treatment, even under hospital conditions with frequent injections of epinephrine, fails and yet the patients are much improved after two or three days' protection in a cubicle. It has also been found that protection for part of a day over a period of some weeks has an after-effect resembling desensitization. It is suggested that this is due to an intake of allergens too small to cause an attack but sufficient to desensitize.

Sir James Crichton-Browne

Sir James Crichton-Browne, F.R.S., the pioneer of neuropathology in this country and for years a leading psychiatrist, has died at the age of 97. Educated at Edinburgh University, where he graduated in 1862, he at once showed a bent for mental diseases by taking appointments at psychopathic hospitals. He became famous by his "West Riding Reports," which emanated from the Wakefield Asylum, Yorkshire. These have become psychiatric classics and their importance in neuropathology was so great that they paved the way for the pioneer work of the neurologists Ferrier, Hughlings Jackson and Horsley. With the two former he joined in the foundation of the British neurologic journal *Brain*. He was one of the earliest advocates of the early treatment of threatened mental breakdown. Well read in literature and a gifted orator, he was for two generations a great figure in public and professional life. He pointed out that a study of childhood afforded the best key to the interpretation of early mental disease.

PARIS

(From Our Regular Correspondent)

Feb. 6, 1938.

Nucleosides and the Circulatory System

At the January 18 meeting of the Académie de médecine of Paris a review of the hormones and vitamins was given by Professor Pouchet of Paris. The study of their composition has been followed by a synthesis of some of the various hormones and vitamins. It was soon found that there existed an intimate interrelation between them. The terms hormones and vitamins have been applied in the past to many extracts of certain organs which are probably simple end products representing disintegration of living cells. The term parahormones was applied to these results of cell metabolism as early as 1911. It has been noticed that the products of disintegration of the albuminoids were capable at different stages of their evolution of exercising a pharmacodynamic action which could be utilized therapeutically. The nucleosides can combine with 1, 2 or 3 molecules of phosphoric acid to form nucleic acids. The latter in turn can be hydrolyzed and, among their products of disintegration, yeast nucleic acid and adenilic acid have been found to be factors in the function of the myocardium; hence their use clinically is indicated in cases of cardiac dysfunction. Yeast nucleic acid has been found in infusions of yeast, blood, urine and pancreas and adenilic acid in those of striated muscle, heart, brain, kidneys and liver. Adenilic acid and especially yeast nucleic acid are active vasodilators. They appear to lessen the work of the heart from a hydraulic point of view. At the same time they regulate cardiac contraction in regularizing the vagosympathetic tonus. The action of adenilic acid and yeast nucleic acid is only transitory but they do not have either a toxic or a cumulative effect on the heart muscle and therefore can be employed indefinitely.

French Congress of Hygiene

The twenty-fourth annual Congress of Hygiene was held Oct. 25-27, 1937, at the Pasteur Institute of Paris. The first symposium was on School Hygiene. In a paper on "Fatigue of School Children," Dr. C. Launay of Paris said that some children present evidence of both physical and mental exhaustion. The former may be the result of adenoids or a primary tuberculous infection, which should be detected by routine medical school inspection. Mental fatigue is usually the result of too many hours in the school room. In the primary schools, at the age of 6 years, the children are obliged to be in classes from five to seven hours a day, each class being of one and a half hour's duration. Only half an hour a week has heretofore been devoted to physical education. In the grammar grades the schedule calls for twenty to twenty-six hours a week in the school room, and in the high school years this rises to from forty-five to fifty hours. Only one or two hours a week is allowed for physical education and this is seldom supervised. Children of poor parents are often obliged to aid in arduous household duties, which causes them to come to school greatly fatigued. The only remedy is to shorten the number of hours in class and devote more time to physical education.

In the second paper, Dr. Armand-Delille called attention to open air schools. The children were in far better mental and physical condition than those in the ordinary school environment.

The causes of lack of adaptation of children in the older classes was the subject of a paper by Drs. Heuyer and de

Lepinay, based on the study of 300 children and adolescents who had been referred to them for psychologic tests because of failure to keep up their school work. In the majority of cases the lack of adaptation was the result of intellectual insufficiency. Some showed mental defects on being subjected to psychologic tests, yet the parents insisted on having the children work for a degree of bachelor of arts, which is given at a much earlier age here than in the United States. Some of those examined showed evidence of a lack of mental equilibrium and inability to concentrate, of such a marked degree that they should never have been permitted to continue their higher studies. The authors strongly emphasized the necessity of examinations by psychologists of all backward children at the end of the primary school years.

Dr. G. Dreyfus-See read a paper on prevention of tuberculosis in schools. A source of infection which it is necessary to eliminate is that of tuberculosis in the teaching personnel, who should be subjected to obligatory annual physical and radiologic examinations. Children who are nonallergic ought to be sent to preventoriums and not be exposed to infection during a period when they are very susceptible. A tuberculin subcutaneous test of all children ought to be made at the beginning of every school year.

In one of the large departments (counties) of western France a radioscopic examination of children in all the rural schools is made with the aid of a portable outfit, according to a paper read by Dr. Jullien. The value of such radioscopic examinations of school children was confirmed by others who took part in the symposium. One of these papers, on the results obtained in the examination of more than 57,000 children in the department of the Moselle, was of special interest. During the school year 1936-1937 tuberculin cutaneous tests were made on 6,525 children from 6 to 14 years of age. The average of positive reactions was 20.8 per cent. Radioscopic examination was carried out in 1,360 children with such a positive cutaneous reaction. Only 13 per cent showed a normal pulmonary condition. The remainder showed evidence of healed, suggestive or active lesions.

Physical Education in French Schools

Persons in charge of public schools here have at last awakened to the necessity of the introduction of more time for sports in the daily curriculum. Until recently, French school children were obliged to attend classes for eight or ten hours a day, so that when they reached the age of 10 to 13 years their physical condition was below that of children in the majority of civilized countries. Up to 1936 the minimum number of class hours per week in the primary grades was thirty, only two hours being devoted to physical education. In many classes no facilities, such as ample playgrounds, existed for carrying out exercises. The result was that mental fatigue was common, owing to the many hours needed for school work with little, if any, allowance for play. During 1936 Mr. Jean Zay, minister of public instruction, made a trial in three of the ninety departments of a plan by which the schedule was to be so arranged that more time should be devoted to physical education. The plan has been so successful that during the school year 1937-1938 it will be followed in twenty-nine departments. One afternoon each week, three hours is devoted to physical education and sports. A second afternoon of every week will include walks, visits to historic sites, gardening and manual training.

The Teachers' Federation has expressed itself as enthusiastic over the results of the experiment as applied to school children below the age of 14 years, so that the plan will soon be made obligatory for all the departments in France. Some additional advantage of this plan are that more attention will be paid in the future to more rigid medical inspection of the children, as well as to more ample provision for swimming pools, showers and more widespread use of lunchrooms in the public schools.

BERLIN

(From Our Regular Correspondent)

Jan. 10, 1938.

Serotherapy of Pneumonia

At the Berlin Medical Society recently the problem of serotherapy of pneumonia was thoroughly discussed. The first speaker was Professor Neufeld, former president of the Robert Koch Infectious Diseases Institute. Reviewing the theoretical bases of serotherapy he stated that animal experimentation was of prime importance for the study of a specific substance. The circumstances which govern pneumonias differ from those of a disease such as diphtheria, for example, wherein as a consequence of the quantitatively constant toxin-antitoxin equilibrium the experimental conditions are always substantially the same. In pneumonia, on the contrary, any one of thirty odd strains of pneumococci may be the pathogenic agent. Accordingly one has no right to speak of "the" antipneumococcus serum. The efficacy of obtainable pneumococcus serums varies greatly according to the strain of micro-organisms involved. For example, the white mouse can be immunized with absolute certainty against type I, whereas the serum of type III must still be considered of little value. The type I pneumococcus represents by far the most common agent of pneumonia in man; type III, although it has been proved extremely pathogenic, is much less frequently encountered. Type III is found chiefly in older and more debilitated persons, whereas types I and II are mostly observed in youthful subjects, of robust constitution. The great difficulties which formerly beset the determination of the guilty strain in a case of pneumonia have been lessened and even entirely obviated by Neufeld's discovery of the "swelling" reaction of pneumococci to specific serums: When pneumococci in sputum are mixed with specific immune serum, there occurs in addition to agglutination a swelling of the peripheral zones of the organisms to double their former size. So precise is the specificity of this capsular swelling that it makes possible the identification of the pathogenic strain within a matter of minutes. The Neufeld reaction represents a great practical advance in the serotherapy of pneumonia. As to the curative effects of the serums, favorable outcome depends largely on the stage of the disease at the time of administration; the later the inoculation, the greater the amount of serum required. In America, highly concentrated serums are utilized to minimize the dangers inherent in inoculation with massive quantities. Intravenous injection has been proved by careful testing to be the suitable method of administration.

If pneumococci are detectable in the blood, the disease will run a severe course and repeated injections of serum will be required. However, in pneumonia the constitutional factors loom larger than the presence of pneumococci. In 50 per cent of otherwise healthy pneumonia patients, pneumococci of various strains can be cultured out of the blood. Exogenous harmful influences such as catching cold, overwork and disturbances of nutrition must be present before the microorganisms become pathogenic. If pneumonia is manifested, the specific antibodies represent the special defense mechanism at the command of the organism.

Dr. Nissen of Copenhagen reported his own observations of the clinical serotherapy of lobar pneumonia. The improvement in diagnoses made possible by the Neufeld reaction test has proved in the Scandinavian countries an impetus to greater utilization of serotherapy. Pneumonia is particularly prevalent in northern Europe; in Copenhagen, for example, the mortality of this disease amounts to 42 per cent. Nissen's administration

of serum to 193 pneumonia patients elicited good results. After the specific strain had been determined and, if possible, within twenty-four hours of the onset, he administered some 40,000 units, usually by intravenous injections. The patients were first tested for possible anaphylaxis. The serum was generally well tolerated. Apart from mild serum sickness, occasionally observed (in 5 per cent), no accessory phenomena were noted. Only in the presence of severe circulatory debility did intravenous administration appear contraindicated. The favorable results elicited by serotherapy are far superior to the results of all other specific curative methods. Success will be achieved, however, only if typing has been carefully done and a sufficient quantity of concentrated serum has been used. Some 50 per cent of Nissen's cases were infected with type I; these represented chiefly patients in the younger age groups. The second largest number (11.5 per cent) were infected with type III and a still smaller number (9.4 per cent) presented type VII. Following inoculation, the clinical course was usually characterized by a marked drop in temperature and above all by a substantial amelioration of the subjective symptoms. High fever is no contraindication of serotherapy.

The exact differentiation of strains was possible in 80 per cent of Nissen's cases by Neufeld's reaction of the sputum. The importance of typing becomes obvious if one compares the favorable results elicited today, with the generally unfavorable results of older serotherapeutic procedures. Certain forms of bronchopneumonia are still refractive to any known type-specific serums. Recently Nissen has begun experimentation with rabbit serum. The use of this substance, he says, has two advantages: economy and the prevention of allergic accessory manifestations. The Danes, having found the favorable results of serotherapy to be so dependent on correct pneumococcus typing, have made the Neufeld test the work of their bacteriologic institutes. These stations also keep on hand adequate stores of serum.

Statistics on Accidental Death

With the increase in traffic, the number of accidental fatalities has mounted. This trend, first discernible in 1933, was still in full swing in the middle of 1937. According to provisional statistics for German communities of 15,000 or more inhabitants, the accident death rate per hundred thousand of population rose from 25 in the year 1933 to 30 in the year 1936. Final figures for 1935 are now complete: In that year a total of 27,783 persons lost their lives through accidents. This number represented an increase of 8.9 per cent over 1934, which latter year showed a 12.2 per cent increase over 1933. Of the accident victims in 1935, 73 per cent were male and 27 per cent female. Traffic accidents were responsible for the largest number of fatalities. Second in importance were fatal accidents related to some peculiar meteorological condition; for example, as the result of a particularly hot summer there were 2,914 drownings in 1935 against 2,582 in 1934. The same factor underlies a more than threefold increase in fatal cases of heat stroke and sunstroke (eighty-three fatalities in 1934 and 255 in 1935). There were also more deaths from lightning (108 in 1934 and 133 in 1935) and from freezing (sixty-one in 1934 and eighty-eight in 1935).

Traffic accidents, especially those which involve the automobile, continued to assume greater importance. In 1935, 48.3 per cent of fatal traffic accidents involved automobiles, 19.6 per cent motorcycles, 10.5 per cent other motor vehicles, 9.8 per cent trains, 2.6 per cent aircraft and 0.1 per cent boats. There were 10,014 fatalities from traffic accidents, one third of all accidental deaths. In contrast to the foregoing data the death rate from murders and other homicides declined again in 1935: there were 854 homicides reported (479 male victims, 375 female victims) as against 928 homicides reported in 1934 (531 male victims, 397 female victims).

ITALY

(From Our Regular Correspondent)

Jan. 22, 1938.

National Congress of Surgery

The Italian Society of Surgery held its forty-fourth congress at Turin under the presidency of Professor Alessandri of the Rome Surgical Clinic.

LATE RESULTS OF OPERATIONS FOR GASTRODUODENAL ULCER

Professor Uffreduzzi of Turin was the principal speaker on late results of operations for gastroduodenal ulcer; his collaborators were Dr. Mairano, Dr. Stoppani and Dr. Foà. The true etiology and nature of the condition are still problematic. In any event, operation is not always followed by favorable results and every surgeon is aware that a certain proportion of patients will present postoperative symptoms indicative of a persistence of the lesion. Uffreduzzi differentiates several types of late postoperative manifestations. Subsequent examination of patients who had undergone gastro-enterostomies in his own service disclosed about 4 per cent who still presented symptoms referable to a persistence of the primitive ulcer. This percentage is decidedly lower than analogous figures reported by other surgeons. The author's follow-up observations of patients who had undergone gastro-entero-anastomosis disclosed about 5 per cent affected with hemorrhages. Similar follow-ups conducted by Alessandri revealed malignant degenerative processes in 2.1 per cent of the patients. Under similar circumstances, Balfour reported the same observation in 6 per cent of his patients. The most serious complication of palliative intervention is the unexpected appearance of a new ulcer at the site of the neostomy or seated on the jejunal mucosa. The incidence of postoperative recidivation of the last named type has been placed by Lewisohn at 34 per cent. Uffreduzzi, although he believes this figure to be too high, admits that the complication is more frequent than it was formerly believed to be. Moreover, the secondary ulcer often leads to further complications, and cases have been seen in which perforation or cancerous degeneration followed its formation. A most prominent sequel of intervention in cases of gastroduodenal ulcer is gastritis, frequently accompanied by modifications in the normal gastro-enteric motility.

Uffreduzzi affirmed that gastro-entero-anastomosis, although at present blamed by many for unsuccessful end results, has elicited a high degree of success and, in better than 50 per cent of the cases, complete and definite cure. Pyloric exclusion, however, is contraindicated. Jejunostomy is indicated in exceptional cases, but the results of limited resections are not always favorable. In virtually all the cases of Uffreduzzi's service in which pylorectomy had been performed according to Juad's method, the author was constrained to perform a second intervention. Nor have favorable results been yielded by resection of the intercostal nerves and section of the gastric branches of the vagus. The problem of palliative resection has assumed a predominant importance in recent years. According to Finsterer the end results in 90 per cent of the cases should be completely favorable. Uffreduzzi dealt with the technic of extensive resections, pointing out how the excision of large segments of the gastric wall has tended effectively to prevent recidivation, especially in predisposed patients, as the procedure counteracts gastric acidity. Conversely, the diminished stomach can be the cause of many disturbances such as anacidity, postoperative anemia and postoperative peptic ulcer. The period required for the patient's organism to adapt itself to the new condition may be protracted. The patient should be observed and the dietary based on a rational reeducation of the stomach. The diet should at first be quantitatively small and not much varied. Anachlorhydria is the chief condition that will require attention. Compensatory, functional adjustments and vicarious activities will be quick to counteract the deficiencies in hydrochloric acid and pepsin. Recidivation

of resectioned ulcer is an extremely rare incident; it occurs in perhaps 1 per cent of the cases. According to the author this complication is in part imputable to the peptic property of the gastric juice and in part to deficient antipeptic property of the gastric mucosa.

Dr. Mairano described the behavior of the digestive secretions following various interventions for gastric ulcer. On the basis of the data reported by other investigators and of his own follow-up observations of the digestive processes of numerous patients, the author concludes that constant modification of the acidity is not an inevitable sequel of gastro-entero-anastomosis. More often there is a decrease in hydrochloric acid or in total acidity. There are rare cases of anachlorhydria, but this condition is almost never dissociated from total acidity. In some patients a persistence of hyperchlorhydria is observed following the intervention and in some cases there is even an exacerbation of this condition, probably the result of incomplete resection or of persistence of the heterotopic zones of the antral mucosa, especially in the duodenum.

Dr. Stoppani described the advances achieved by roentgenologic studies of the gastric mucosa, the entire stomach and the upper part of the jejunum. From a roentgenologic standpoint, the problem following excisions in the lesser curvature is to determine whether the stomach can maintain its functional capacity or whether it presents alterations that render further roentgenologic studies unnecessary.

Dr. Foà for the last ten years has had experience in the management of patients with duodenal ulcer at the Turin Surgical Clinic before and after operation. As most satisfactory technical methods of visualization, he mentioned studies obtained after the patient has ingested a light meal, visualization of the mucous plicae of the gastroduodenaljejunal regions, and serialographs obtained with dosed compression.

LATE RESULTS OF THE SURGICAL TREATMENT OF URINARY LITHIASIS

Prof. Domenico Taddei of the Florence Surgical Clinic reported his observations on the sequels of nephrectomy, conservative kidney operations, cystostomy and lithotresis. According to Taddei, nephrectomy is indicated in the presence of such signs as ectasia, suppuration or sclerosis and if the other kidney is healthy. The remaining kidney usually functions well and the defect gives rise to no incidents in case of pregnancy, further surgical operation or intercurrent illnesses. Nephrectomy is still performed in about one third of the cases. Postoperative persistence of pyuria, fistulas or refluxes are rarely observed. Subsequent calculosis of the remaining kidney is an unusual incident, occurring in about 5 per cent of the cases.

Renal and pyelic calculoses in which conservative treatment is indicated are usually of the aseptic type or of the type characterized by mild infection, a single or a few localized concretions with little alteration of the kidney and little or no ectasis of the excretory passages. The criteria of operability differ among surgeons. Whereas in a limited number of cases a virtually complete recovery can take place, in a majority of cases, the postoperative course is marked by a persistence of infections, ectasia and functional incapacity. Recidivation, especially in calculosis of the calix, is frequent. Roentgenography as a visual aid during actual operation represents a great advance. Since 1928 Taddei has advocated a technical procedure of his own device, which is at the disposal of any surgeon. Postoperative treatment of patients, directed at conservation of renal functional capacity, is based on the as yet relatively unsolved etiologic problem of calculosis. Today this question is more complex than ever, since both infection and diathesis are considered to be factors. Among other factors suggested by present-day investigators are the urinary p_H, colloidal condition of urinary salts, endocrine disorders and avitaminosis.

Indications for pyelotomy are simple: absence of parenchymal lesions, single calculus of the pelvis, and slight retention. Also for nephrotomy there are particular indications. The width of renal incision is apparently of little importance in postoperative functional incapacity since the latter condition depends rather on other factors such as infections, ectasia and sclerosis. In many cases it is preferable to abstain; in others, conservative operations are indicated. In cases presenting pyonephrosis, nephrectomy may be imperative.

PATHOLOGY AND THERAPY OF THE NEUROHYPOPHYSIAL SYNDROME

The third subject was discussed in joint session with the Society of Internal Medicine. Professor Di Guglielmo, representing the internists, differentiated two categories of neurohypophysial syndromes, the endosellar and the juxtasellar. The first group comprises the syndromes of hyperpituitarism, both acidophil and basophil. To the second group belong the syndromes of hypopituitarism and of apituitarism (Simmond's disease). The author took up the diagnostic criteria of the various forms. The most important medical therapeutic procedure is incretotherapy; pluriglandular parenteral application is most effective, especially if combined with treatment of other coexistent factors such as syphilis or tuberculosis. The curative results of this procedure are of an ephemeral nature, however, since after a certain time an antihormone effect is manifested. In treatment of the syndromes of apituitarism, sometimes spectacular results can be elicited by prolonged administration of various glandular extracts from the anterior lobe of the hypophysis, the thyroid, the gonads and the adrenal cortex.

Professor Chiasserini spoke of sellar and parasellar aneurysms and of the usual treatment of these, which consists of ligation of the internal carotid at the neck. The most common hypophysial tumors are adenomas of the anterior lobe; these are differentiated, cytologically as chromophobic (agranulocytic) and chromophilic (granulocytic); the latter may be subdivided into eosinophilic and basophilic. Eosinophilic adenomas form the anatomic basis of acromegaly and of acromegalic gigantism. Basophilic adenomas can produce the chiasmatic syndrome described by Cushing, which is characterized by bitemporal hemianopia, primary optic atrophy and roentgenologically demonstrable modifications of the sella turcica. The x-ray visualizations are of fundamental diagnostic importance, since they demonstrate virtually any enlargement of the sella, the so-called sellar expansion.

Chiasserini outlined both the palliative and the radical surgical treatment of hypophysial tumors. The most suitable palliative interventions are subtemporal decompression and hypophysial puncture. At present the operative approach of predilection is by way of the frontal bone and the sphenoid.

Marriages

JAMES H. HOLLIMON, Houston, Texas, to Miss Lora Sherman of Picayune, Miss., Oct. 6, 1937.

SPENCER T. TRICE, Talco, Texas, to Miss Hazel Dell Graham of Texarkana, Nov. 13, 1937.

HAROLD F. LANSHE to Miss Pauline McKissick, both of Harrisburg, Pa., January 5.

CLARK R. ROMINGER, Cresco, Iowa, to Miss Alice Jensen of Valley, Neb., Dec. 30, 1937.

GEORGE H. STEELE, Belmond, Iowa, to Miss Inga Hill of Aurora, Minn., January 4.

ROLAND D. PORTER, Abington, Pa., to Miss Gertrude S. Reed of Pottstown recently.

JOHN M. PRESTON to Mrs. Lula W. Ellis, both of Lancaster, S. C., Dec. 4, 1937.

Deaths

William Edgar Darnall ⊕ Atlantic City, N. J.; University of Virginia Department of Medicine, Charlottesville, 1895; Secretary of the Section on Diseases of Children of the American Medical Association, 1900-1901, and fourth Vice President in 1914; member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons and the American Clinical and Climatological Association; fellow of the American College of Surgeons; member of the state board of medical examiners; gynecologist to the Atlantic City Hospital and consulting gynecologist to the Municipal Hospital; aged 68; died, Dec. 27, 1937, of coronary occlusion.

Levy Millspaugh Hathaway ⊕ Colonel, U. S. Army, retired, Owensboro, Ky.; University of Virginia Department of Medicine, Charlottesville, 1901; entered the army as an assistant surgeon in 1902; promoted through the various grades to that of colonel in 1928; retired in 1933 for disability in line of duty; was awarded the Distinguished Service Medal for meritorious service during the World War; fellow of the American College of Surgeons; aged 60; died, Dec. 14, 1937.

Truman James Allen ⊕ Brandon, Vt.; University of Vermont College of Medicine, Burlington, 1912; associate professor of neurology at his alma mater; member of the American Psychiatric Association and the New England Society of Psychiatry; medical superintendent of the Brandon State School; on the staffs of the Mary Fletcher Hospital, Burlington, and the Rutland Hospital; aged 49; died, Dec. 29, 1937.

Clarence Martin ⊕ St. Louis; Barnes Medical College, St. Louis, 1898; member of the American Urological Association; on the staffs of the Missouri Baptist, Josephine Heitkamp Memorial, St. Louis County and St. Louis City hospitals; served during the World War; editor-in-chief of the *Urologic and Cutaneous Review;* aged 60; died, Dec. 7, 1937, in the Jewish Hospital, following a gallbladder operation.

Esther L. Blair, Pittsburgh; Woman's Medical College of Pennsylvania, Philadelphia, 1890; physician to women, Carnegie Institute of Technology; member of the Medical Society of the State of Pennsylvania; physician to the American Red Cross during the World War; aged 75; died, Dec. 11, 1937, in the Orange (N. J.) Memorial Hospital, of myelogenous leukemia and arteriosclerosis.

Robert Valentine Boyce, Hartford, Conn.; University of Vermont College of Medicine, Burlington, 1913; member of the Connecticut State Medical Society and the New England Obstetrical and Gynecological Society; served during the World War; past president of the city board of health; aged 47; on the staff of St. Francis Hospital, where he died, Dec. 29, 1937, of pneumonia.

Ralph J. Levy ⊕ New York; New York Homeopathic Medical College and Flower Hospital, New York, 1914; formerly assistant professor of gynecology and obstetrics at his alma mater; fellow of the American College of Surgeons; attending obstetrician and gynecologist to the Broad Street and Park East hospitals; aged 49; was found dead, Dec. 12, 1937.

Frederick McKendrie Lowe, Kansas City, Mo.; Rush Medical College, Chicago, 1903; member of the Missouri State Medical Association; formerly associate professor of physiology at the University Medical College of Kansas City; for many years on the staff of the General Hospital; aged 66; died, Dec. 20, 1937, of peritonitis and carcinoma of the cecum.

Burton Sylvander Booth, Troy, N. Y.; Albany (N. Y.) Medical College, 1889; member of the Medical Society of the State of New York; fellow of the American College of Surgeons; veteran of the Spanish-American and World wars; consulting laryngologist to the Leonard Hospital; aged 69; died, Dec. 2, 1937, of heart disease.

Isadore Goldstein ⊕ New York; Cornell University Medical College, New York, 1904; member of the American Academy of Ophthalmology and Oto-Laryngology; on the staffs of the New York Eye and Ear Infirmary, Sydenham Hospital and the Mount Sinai Hospital; aged 59; died, Dec. 23, 1937.

Samuel Ginsburg, Norwich, Conn.; Jefferson Medical College of Philadelphia, 1908; member of the Connecticut State Medical Society, American Psychiatric Association and the New England Society of Psychiatry; on the staff of the Norwich State Hospital; aged 53; died, in December, at New York.

Willard C. Kendig, Cincinnati; Medical College of Ohio, Cincinnati, 1891; formerly assistant physician to the Longview Hospital; for many years examining physician to the Probate Court; aged 68; died, Dec. 25, 1937, in the Jewish Hospital, of cerebral arteriosclerosis and chronic nephritis.

Rafael Lopez Sicardo, San Juan, P. R.; College of Physicians and Surgeons, Baltimore, 1907; chairman of the Puerto Rico Insular Board of Health; member of the Medical Association of Puerto Rico; medical superintendent of the Capital City Hospitals; aged 62; died, Dec. 22, 1937.

Gilbert Newton Lehr, Rome, N. Y.; University of the City of New York Medical Department, 1880; member of the Medical Society of the State of New York; formerly county coroner; on the staff of the Rome Hospital; aged 80; died, Dec. 23, 1937, of heart disease and nephritis.

William Gordon Bodie ⊕ Wagener, S. C.; Medical College of the State of South Carolina, Charleston, 1916; served during the World War; formerly county health officer; aged 45; died, Dec. 31, 1937, in the Baptist Hospital, Columbia, of injuries received when struck by an automobile.

Samuel Albert Lundy, Fort Worth, Texas; Fort Worth School of Medicine, Medical Department of Texas Christian University, 1911; member of the State Medical Association of Texas; served during the World War; aged 58; died suddenly, Dec. 11, 1937, of coronary occlusion.

Charles P. Dolan, Worthington, Minn.; State University of Iowa College of Medicine, Iowa City, 1880; member of the Minnesota State Medical Association; for many years county coroner, and health officer of Worthington; aged 80; died, Dec. 23, 1937, of hypostatic pneumonia.

Alexander Crane Eastman, Sarasota, Fla.; Harvard University Medical School, Boston, 1900; served during the World War, formerly on the staffs of the Mercy and Springfield hospitals, Springfield, Mass.; aged 62; died, Dec. 23, 1937, of chronic staphylococci septicemia.

Donnie Arnold Burress, High Point, N. C.; Louisville (Ky.) and Hospital Medical College, 1908; formerly on the staff of the Burrus Memorial Hospital; aged 57; died, Dec. 2, 1937, in Guilford County Sanatorium, Jamestown, of actinomycosis of the lungs.

Wilson C. Martin, Mocksville, N. C.; College of Physicians and Surgeons, Baltimore, 1888; past president and secretary of the Davie County Medical Society; member of the county board of health; aged 72; died, Dec. 5, 1937, of carcinoma of the sigmoid.

William Lucien Heizer Sr., Lexington, Ky.; Hospital College of Medicine, Louisville, Ky., 1905; member of the Kentucky State Medical Association; formerly state registrar of vital statistics; aged 57; died, Dec. 9, 1937, of coronary occlusion and nephritis.

John W. Bowers, South Portland, Maine; College of Physicians and Surgeons, Baltimore, 1882; member of the Maine Medical Association; aged 76; died, Dec. 7, 1937, in the Maine General Hospital, Portland, of heart disease, stricture of the ureter and uremia.

Charles Emmanuel Kaufman, West Haven, Conn.; Yale University School of Medicine, New Haven, 1920; member of the Connecticut State Medical Society; health officer of West Haven; aged 51; died, Dec. 3, 1937, of coronary occlusion and arteriosclerosis.

Robert Edgar Hughson, Yorkville, Ohio; Ohio State University College of Medicine, Columbus, 1931; member of the Ohio State Medical Association; aged 34; on the staff of the Martins Ferry (Ohio) Hospital, where he died, Dec. 21, 1937, of uremia.

George Riley Keen, Scottsville, Ky.; University of Tennessee Medical Department, Nashville, Tenn., 1900; member of the Kentucky State Medical Association; aged 64; died, Dec. 5, 1937, in the Protestant Hospital, Nashville, of carcinoma of the liver.

Samuel John House, Brentwood, Tenn.; Rush Medical College, Chicago, 1921; formerly assistant professor of clinical medicine at the Vanderbilt University School of Medicine, Nashville; served during the World War; aged 45; died, Dec. 26, 1937.

Marion L. Albro Gleason, Providence, R. I.; Tufts College Medical School, Boston, 1907; director of child welfare, department of public health; aged 65; died, Dec. 3, 1937, in the Homeopathic Hospital, of coronary occlusion and diabetes mellitus.

William Franklin Burres, Urbana, Ill.; Rush Medical College, Chicago, 1882; member of the Illinois State Medical Society; formerly member of the state legislature and mayor of Urbana; aged 80; died, Dec. 19, 1937, of arteriosclerotic heart disease.

Fred Carl Schreiber, San Francisco; University of Kansas School of Medicine, Kansas City, 1926; member of the Associated Anesthetists of the United States and Canada; aged 44; died, Nov. 12, 1937, of rheumatic endocarditis and pulmonary edema.

Samuel Milton Black, Georgetown, Ill.; University of Nashville (Tenn.) Medical Department, 1899; formerly health officer, mayor, member of the board of education and bank president; aged 69; died, Dec. 20, 1937, of tuberculosis of the lungs.

Charles James Hamilton, Cornwall, Ont., Canada; University of Toronto Faculty of Medicine, Toronto, 1879; Victoria University Medical Department, Coburg, 1880; for many years medical officer of health and coroner; aged 82; died, Dec. 19, 1937.

Darell Martin Busby, Phoenix, Miss.; Mississippi Medical College, Meridian, 1909; Memphis (Tenn.) Hospital Medical College, 1913; member of the Mississippi State Medical Association; aged 53; died, Dec. 27, 1937, of cerebral hemorrhage.

Joel Augustus Dawson Jr., New Orleans; Tulane University of Louisiana School of Medicine, New Orleans, 1937; intern at the Touro Infirmary; aged 28; died, Dec. 20, 1937, in Mobile, Ala., of teratoma of the right testicle with metastases.

Antonio G. Maltese, Chicago; Regia Università di Napoli Facoltà di Medicina e Chirurgia, Italy, 1903; member of the Illinois State Medical Society; served during the World War; aged 58; died suddenly, Dec. 17, 1937, of angina pectoris.

Lucien Hayden Guptill, Boston; Medical School of Maine, Portland, 1877; University of the City of New York Medical Department, 1878; aged 83; died, Nov. 15, 1937, of arteriosclerosis, cerebral hemorrhage and hypostatic pneumonia.

Edward Turner Bramlitt, Malvern, Ark.; Louisville (Ky.) Medical College, 1876; member of the Arkansas Medical Society; past president of the Hot Spring County Medical Society; aged 83; died, Dec. 18, 1937, of injuries received in a fall.

George B. Durand, Waupun, Wis.; Homeopathic Hospital College, Cleveland, 1874; formerly city health officer; aged 84; died, Dec. 23, 1937, in the Wisconsin General Hospital, Madison, of bronchopneumonia, uremia and diabetes mellitus.

John Lewis Lane, Tuckerton, N. J.; Jefferson Medical College of Philadelphia, 1888; mayor of Tuckerton; at various times county coroner and member of the board of education; aged 71; died, Dec. 2, 1937, of cerebral hemorrhage.

Omer E. Dale, Everton, Ind.; Barnes Medical College, St. Louis, 1900; member of the Indiana State Medical Association; veteran of the Spanish-American War; aged 61; died, Dec. 24, 1937, of injuries received in an automobile accident.

Herbert Roney Drewry, Norfolk, Va.; Medical College of Virginia, Richmond, 1895; member of the Medical Society of Virginia; served during the World War; aged 70; died, Dec. 1, 1937, of hypertensive cardiovascular disease.

Norfleet Mann Gibbs, New Bern, N. C.; University of Maryland School of Medicine, Baltimore, 1896; member of the Medical Society of the State of North Carolina; aged 65; died, Dec. 25, 1937, of arteriosclerosis and hypertension.

Pellegrino Dacunto, Newark, N. J.; Regia Università di Napoli Facoltà di Medicina e Chirurgia, Italy, 1898; member of the Medical Society of New Jersey; aged 70; died, Dec. 28, 1937, of coronary sclerosis and cerebral embolism.

Benjamin T. Black, Campbellsville, Ky.; University of Louisville Medical Department, 1885; member of the Kentucky State Medical Association; for many years county coroner; aged 73; died, Dec. 30, 1937, of pneumonia.

Forrest Lee Lewis, Camilla, Ga.; Atlanta Medical College, 1892; mayor; aged 69; died, Dec. 12, 1937, in the Crawford W. Long Memorial Hospital, Atlanta, of coronary thrombosis following resection of the prostate.

Glenford Albert Mowat, Campbellton, N. B., Canada; McGill University Faculty of Medicine, Montreal, Que., 1929; served during the World War; aged 39; died, Nov. 5, 1937, in the Soldiers' Memorial Hospital.

J. Stow Ballard, Berkeley, Calif.; Hahnemann Medical College and Hospital of Philadelphia, 1889; aged 75; died, Dec. 8, 1937, of carcinoma of the prostate with metastasis to bones and hypostatic pneumonia.

James Craig Mazique, Natchez, Miss.; Howard University College of Medicine, Washington, D. C., 1897; aged 67; died, Dec. 12, 1937, in the Natchez Sanatorium, of diabetes mellitus, gangrene and arteriosclerosis.

John Hoch, West Long Branch, N. J.; College of Physicians and Surgeons, Medical Department of Columbia College, New York, 1892; aged 68; died, Dec. 21, 1937, of cerebral hemorrhage and arteriosclerosis.

Robert Roy Hoskins, Mathews, Va.; Medical College of Virginia, Richmond, 1903; member of the Medical Society of Virginia; served during the World War; aged 60; died, Dec. 20, 1937, of cerebral hemorrhage.

Robert Bennett Cuthbert, Trenton, Ga.; Hahnemann Medical College and Hospital of Philadelphia, 1895; aged 71; died, Dec. 17, 1937, in a hospital at Chattanooga, Tenn., of ruptured peptic ulcer and peritonitis.

Henry H. Lucas ✠ Paterson, N. J.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1895; on the staff of St. Joseph's Hospital; aged 73; died, Dec. 9, 1937, of multiple abscess of the liver.

Anthony Abraham Deep ✠ Washington, D. C.; George Washington University School of Medicine, Washington, 1924; aged 39; was found dead, Dec. 12, 1937, of illuminating gas poisoning, self administered.

John W. Vick, Marion, Ill.; Vanderbilt University School of Medicine, Nashville, Tenn., 1894; member of the Illinois State Medical Society; aged 88; died, Nov. 26, 1937, of myocarditis and arteriosclerosis.

Albert Newton Doyle, Minor Hill, Tenn.; University of Tennessee Medical Department, Nashville, 1888; member of the Tennessee State Medical Association; aged 71; died, Dec. 13, 1937, of pneumonia.

Mendel Volkenheim ✠ New Britain, Conn.; Yale University School of Medicine, New Haven, 1908; on the staff of the New Britain General Hospital; aged 52; died, Nov. 6, 1937, of coronary occlusion.

Margarito Montemayor, San Antonio, Texas; Universidad Nacional Facultad de Medicina, Mexico, D.F., 1905; aged 61; died, Nov. 9, 1937, in the Physicians and Surgeons Hospital, of coronary sclerosis.

Frederick Michael Boyle, Buffalo; Niagara University Medical Department, Buffalo, 1893; served during the World War; aged 70; died, Dec. 2, 1937, of aneurysm of the aorta and arteriosclerosis.

Edgar Burr Babcock, Kalkaska, Mich.; Michigan College of Medicine, Detroit, 1884; for many years member of the local school board; formerly postmaster; aged 80; died, Dec. 6, 1937, of arteriosclerosis.

Joseph William Long ✠ Walkersville, Md.; Hahnemann Medical College and Hospital of Philadelphia, 1903; served during the World War; aged 58; died, Dec. 14, 1937, of coronary thrombosis.

Thomas Alexander Cox, Hertford, N. C.; University of Maryland School of Medicine, Baltimore, 1892; formerly county coroner; aged 69; died, Dec. 13, 1937, in Jackson, Miss., of pneumonia.

Elmer Oscar Steeves, Rugby, N. D.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1903; aged 60; died, Nov. 19, 1937, of coronary thrombosis and hypertensive heart disease.

A. W. Thompson, Kansas City, Mo.; Barnes Medical College, St. Louis, 1904; formerly superintendent of the Kansas City General Hospital; aged 65; died, Nov. 17, 1937, of cerebral hemorrhage.

Arie U. Klock, Ames, N. Y.; Albany Medical College, 1886; member of the Medical Society of the State of New York; aged 75; died, Dec. 10, 1937, of heart disease and cerebral hemorrhage.

Lyman E. Baker, Mechanicsburg, Ohio; Cleveland Medical College, 1895; aged 67; died, Dec. 22, 1937, in the Grant Hospital, Columbus, of hypertensive heart disease and chronic nephritis.

Henry William Straus ✠ Brooklyn; College of Physicians and Surgeons, Baltimore, 1913; on the visiting staff of the Jewish Hospital; aged 46; died, Nov. 21, 1937, of chronic nephritis.

Harry Andrews Rosenthal, Clarksburg, W. Va.; College of Physicians and Surgeons, Baltimore, 1902; member of the West Virginia State Medical Association; aged 61; died, Nov. 12, 1937.

William Rufus Apple, Paris, Ill.; Northwestern University Medical School, Chicago, 1911; aged 59; died, Dec. 11, 1937, in St. Anthony's Hospital, Terre Haute, Ind., of heart disease.

Carl Bonning, Detroit; Université de Strasbourg Faculté de Médecine, Germany, 1882; member of the Michigan State Medical Society; aged 82; died, Dec. 23, 1937, of coronary thrombosis.

John Taylor Steele ⊕ Dunsmuir, Calif.; Manitoba Medical College, Winnipeg, 1924; on the staff of the Dunsmuir Hospital and Sanatorium; aged 38; was accidentally drowned, Nov. 28, 1937.

Herbert Augustus Abbott, San Francisco; University of Nebraska College of Medicine, Omaha, 1896; aged 68; died, Dec. 3, 1937, of myocarditis, arteriosclerosis and hypertension.

David E. Winer, Vanderbilt, Mich.; Saginaw (Mich.) Valley Medical College, 1903; aged 64; died, Nov. 28, 1937, in the Grayling (Mich.) Mercy Hospital, of mesenteric thrombosis.

Caroline Nielsen Conner, St. Ignace, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1876; aged 90; died, Dec. 21, 1937, of cerebral hemorrhage.

James Switzer Freeborn, Magnetawan, Ont., Canada; Victoria University Medical Department, Coburg, 1885; L.K.Q.C.P., Ireland, 1887; aged 79; died, Nov. 8, 1937.

William A. Burnham, Boulder, Colo.; Rush Medical College, Chicago, 1877; aged 89; died, Dec. 28, 1937, in the Community Hospital, of arteriosclerosis and bronchopneumonia.

Albert Sidney Johnston Smith, San Jose, Calif.; Washington University School of Medicine, St. Louis, 1893; aged 68; died, Nov. 13, 1937, of carcinoma of the stomach.

Edmund Willoughby Wilson, Rolfe, Iowa; State University of Iowa College of Medicine, Iowa City, 1896; aged 69; died, Nov. 24, 1937, in San Diego, of heart disease.

John M. Slaymaker, Philadelphia; Jefferson Medical College of Philadelphia, 1883; aged 76; died, Nov. 30, 1937, in the Joseph Price Memorial Hospital, of pneumonia.

Hugh **Alexander Elliot,** Toronto, Ont., Canada; University of Toronto Faculty of Medicine, 1916; aged 45; died, Nov. 16, 1937, of progressive muscular atrophy.

John C. Shepherd, Rulo, Neb.; University of Louisville (Ky.) Medical Department, 1876; aged 83; died, Nov. 7, 1937, of arteriosclerosis and chronic myocarditis.

John **Stenhouse,** Toronto, Ont., Canada; University of Toronto Faculty of Medicine, 1894; aged 76; died, Nov. 26, 1937, in the Victoria Memorial Hospital.

W. Frank Snider, Liberty, Ill.; Hospital College of Medicine, Louisville, Ky., 1889; aged 73; died, Nov. 5, 1937, in Clayton, of chronic nephritis and uremia.

Robert **Crees,** Napa, Calif.; University of California Medical Department, San Francisco, 1894; aged 78; died, Dec. 6, 1937, of a self-inflicted bullet wound.

Wendell Warden Carrothers, Galt, Ont., Canada; Western University Faculty of Medicine, London, 1920; aged 45; died, Nov. 27, 1937, of pneumonia.

Allen **Moorman,** Redfield, Iowa; State University of Iowa College of Medicine, Iowa City, 1896; aged 66; died, Nov. 3, 1937, of Hodgkin's disease.

R. L. Stewart, Koran, La.; College of Physicians and Surgeons, Dallas, Texas, 1908; aged 59; died, Nov. 23, 1937, of carcinoma of the rectum.

Charles Olivier Milot, Montreal, Que., Canada; University of Montreal Faculty of Medicine, Montreal, 1922; aged 45; died, in November 1937.

Henry Hicks Coleman, Moncton, N. B., Canada; University of the City of New York Medical Department, 1877; aged 84; died, Nov. 22, 1937.

Jerome F. Honsberger, Kitchener, Ont., Canada; Trinity Medical College, Toronto, 1886; L.R.C.P., London, 1886; aged 78; died, Nov. 9, 1937.

Richard Mason Lipsey, St. Thomas, Ont., Canada; University of Toronto Faculty of Medicine, 1894; aged 73; died, Nov. 25, 1937.

Louis Joseph Desy, Montreal, Que., Canada; Laval University Medical Faculty, Montreal, 1889; died, Dec. 7, 1937, in Paris.

Moses L. Ship, Montreal, Que., Canada; McGill University Faculty of Medicine, Montreal, 1902; aged 59; died, Nov. 3, 1937.

Moses Bulian ⊕ Boston; Dragomanov Institute, Kiev, Russia, 1912; aged 51; died, Nov. 17, 1937, of coronary thrombosis.

John F. Long, Luray, Va.; Medical College of Virginia, Richmond, 1873; aged 88; died, Dec. 8, 1937, of heart disease.

L. H. Smith, Atlanta, Ga. (licensed in Georgia in 1899); aged 68; died, Nov. 30, 1937, of uremia and mitral stenosis.

Thomas Henry Mott, Victoria, B. C., Canada; Trinity Medical College, Toronto, Ont., 1884; died, Nov. 13, 1937.

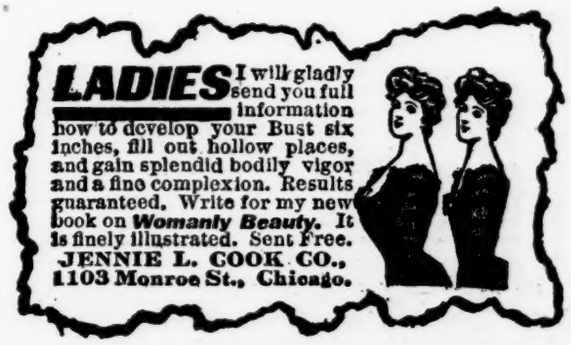
Bureau of Investigation

CURTIS A. DAVIS

Another Bust-Developer Fraud Is Barred from the Mails

"Youth-Aid Products," a swindling mail-order concern run by Charles A. Davis of Los Angeles, was the object of a fraud order issued by the Post Office Department in July 1937. This trade name was adopted by Davis some time subsequent to January 1936, when a fraud order was issued against a Davis scheme known as the "Jennie L. Cook Company." It was to evade the 1936 order that Davis assumed the name of "Youth-Aid Products." The business was the same under both names —selling an alleged bust-developer.

Davis is an old offender. More than twenty years ago he was carrying on mail-order frauds in Chicago under various trade names. Because of the flagrant misrepresentation made by Davis at that time for the articles he offered for sale, a fraud order was issued on Aug. 7, 1916, against his various trade names. Davis evaded the order by changing most of the names under which he had been doing business; so, five months later —Jan. 25, 1917—the post office authorities issued a supplemental order against the new names. Even that did not stop Davis, for he adopted still other names. He continued his business until the postal authorities issued a further supplemental fraud order on Feb. 8, 1917, on the later names.


LADIES I will gladly send you full information how to develop your Bust six inches, fill out hollow places, and gain splendid bodily vigor and a fine complexion. Results guaranteed. Write for my new book on Womanly Beauty. It is finely illustrated. Sent Free.
JENNIE L. COOK CO.,
1103 Monroe St., Chicago.

Sometime in the interim between 1917 and 1937 Davis transferred his activities from Chicago to Los Angeles. He is now more than 67 years old but still evidently believes that mail-order frauds are profitable and that the risk of criminal prosecution is negligible. In Los Angeles he used for some years the trade name "Jennie L. Cook Company." He claims, so the post office officials report, that Jennie L. Cook is the name of a sister who resided next door to the rooming house from which Davis conducted his fraudulent business. Davis is said to have stated that his sister had no financial interest in the fraud.

Just when Davis started the Los Angeles Cook concern fraud does not appear. It is of record, however, that in 1932 the Federal Trade Commission issued a Cease and Desist Order against Curtis A. Davis trading as the Jennie L. Cook Company of Los Angeles. In this Curtis was ordered to (1) cease advertising as a woman; (2) cease implying in his advertising that the statements he made were from one woman to another; (3) cease claiming that the Jennie L. Cook Company was composed of Parisian beauty culturists; (4) cease advertising that the Cook "treatment" was scientific, was made from a French formula, was a constitutional vitalizer and a tissue builder; (5) cease claiming that by the use of the "treatment" a perfect figure could be developed and the human body could be properly proportioned, and (6) cease claiming that the "treatment" would fill up hollows in the body, give the user strength and remove wrinkles. The facts were briefly noted in this department of THE JOURNAL, April 30, 1932.

So much for 1932. But Davis evidently considered that the commission's order was meant in a pickwickian sense, for in 1936 he was still at the same old stand, operating under the same name and with practically the same claims when the post office officials served notice on him.

According to the memorandum of the Solicitor of the Post Office Department to the Postmaster General recommending the issuance of a fraud order, each bust-developer treatment sold by Davis cost him thirty-five cents and was sold for three dollars. Davis, according to the memorandum, did not advertise in magazines or newspapers, but he obtained his victims by purchasing "sucker lists" from the Chart Letter Company, Chicago, and the Rose Miller Company, Birmingham, Ala.

In December 1935 the post office officials personally served Curtis A. Davis with a citation calling on him to show cause by Jan. 3, 1936, why a fraud order should not be issued against the Jennie L. Cook Company. Curtis appears to have ignored utterly the government's action, for the authorities reported that they received no answer to the citation nor did Curtis appear either in person or by attorney, at the hearing. The Solicitor for the Department—Judge Karl A. Crowley—thereupon reviewed the evidence collected by the postal inspectors and concluded that the Jennie L. Cook Company was a scheme for obtaining money through the mails by means of false and fraudulent pretenses, representations and promises. Solicitor Crowley recommended the issuance of a fraud order closing the mails to the company. It was issued Jan. 11, 1936.

But this apparently did not worry Curtis. He evaded the order by the simple device of adopting a new name—"Youth-Aid Products." A year and a half later (July 9, 1937) the post office authorities issued a supplemental fraud order covering "Youth-Aid Products." Just what mail-order racket Curtis A. Davis will next indulge in is known, probably, only to Curtis.

This brief statement of facts is of importance more because of its social and economic implications than because of the sordid details with which it deals. It is one more example of the inadequacy of our laws in protecting the public against medical fraud.

Correspondence

THE ROLE OF INSULIN IN THE PSYCHOSES

To the Editor:—Dr. H. M. Smith (THE JOURNAL, June 5, 1937, p. 1959), commenting on insulin therapy for schizophrenia, says "the coma results from the reaction to insulin rather than from the hypoglycemia." Sakel's own curves (Neue Behandlungsmethode der Schizophrenie) indicate blood sugar values which are moderately high (usually in the neighborhood of 60 mg. per hundred cubic centimeters) even though large enough doses to bring on coma were administered. Certainly the possibility is not excluded that an extrahypoglycemic factor may be producing the favorable results of this therapy. If the hypoglycemia were not an essential feature of the treatment, both the hazards and the great expense of insulin therapy might be largely overcome.

The primary functions of insulin in the normal person have not been entirely established. It stores glycogen in the liver and in the muscles. There is some question as to an increased oxidation in the peripheral tissues. However this may be, the hypoglycemia is truly secondary. If the responsible therapeutic factor in the Sakel treatment is the insulin itself and not the secondary hypoglycemia, it might be possible to secure the same effects by giving frequent nourishment or ample dextrose simultaneously with the islet hormone. This problem is being investigated at the present time.

Although it has been stated that the best results are obtained in schizophrenia when shock is prolonged (from three to five hours), no controls have been tested. Before the advent of shock therapy, favorable psychiatric effects were occasionally reported from small doses of insulin. May not the larger doses utilized be directly responsible for the better results?

EUGENE ZISKIND, M.D. DOUGLAS DRURY, M.D.
ESTHER SOMERFELD, M.D. PAUL GREELEY, M.D.
Los Angeles.

DOSAGE OF DIGITALIS

To the Editor:—In the article by Stroud and Vander Veer on digitalis (THE JOURNAL, Nov. 27, 1937, page 1809, second column, first paragraph) it is stated that the dry digitalis preparations are to be preferred to the tincture for the reason, among others, that the dose is much more accurate "since even with the standard minim dropper the patient is apt to miscount the number of drops." The inference could be easily drawn from this that correct counting with the standard minim dropper would give correct dosage. Presumably the dropper referred to was the one made official in this country on June 1, 1936, which delivers 80 drops of water in 4 cc. but requires from 160 to 180 drops of tincture of digitalis to produce a bulk measure of 4 cc.

A footnote states that "a dose in drops from an ordinary dropper has from two to three times the number of drops as the same amount measured in minims." In this connection it is well to recall that there is at least one dropper furnished with a special tincture of digitalis that practically delivers a minim per drop.

It was freely predicted that the introduction of a standard dropper would add to the confusion about drops and droppers, particularly in giving liquid digitalis preparations. It may become necessary to define this dropper as a medicine dropper, official, U. S. P. XI, for water, but with *tinctures* delivers only one third of a minim per drop.

SINCLAIR LUTON, M.D., St. Louis.

UREA FOR WOUND HEALING

To the Editor:—The recent discovery of the use of urea in the healing of wounds has been mentioned in THE JOURNAL. It might be of interest to younger physicians to know that this discovery was anticipated by farmers a generation ago. In about 1885 I was at the home of a neighbor and he was treating a case of fistulous withers in a horse with his own urine. He told me, "It will heal it right up." I told this to a class a short time ago and one of the members said that in his part of the country farmers husking corn barehanded used this same lotion on their hands to keep them from getting sore, and they could husk corn all the fall with no gloves or mittens.

C. J. ELMORE, Liberty, Mo.
Professor of Biology, William Jewell College.

COMMENT.—Macalister in 1912 noted the use of comfrey root by the natives of rural England, who applied it to wounds to promote healing. Macalister used a rather strong infusion of the comfrey root in the successful treatment of an extensive rodent ulcer of the chest which under all other methods had continued to grow more extensive. Chemical analysis revealed that the substance contained from 0.8 to 0.9 per cent of allantoin. Subsequently it has been recognized and is described in the British Pharmaceutical Codex under the name Symphytum, with the synonym comfrey root. It is stated to be the dried rhizome and root of Symphytum officinale (Boragianaceae). It is stated to contain from 0.6 to 0.8 per cent of allantoin. Allantoin itself is a British Pharmaceutical Codex item and both preparations are described as cell proliferants in Martindale's Extra Pharmacopeia.

About the time allantoin was being prepared for the pharmaceutical market, Robinson carried his experimentation one step further and reported that a constituent derived from allantoin was probably responsible for its effectiveness. The product is urea and it is even less expensive than allantoin. Urea, which is manufactured in enormous quantities, is readily available.

An article appearing in THE JOURNAL, April 3, 1937, by Holder and MacKay, notes that Symmers and Kirk more than twenty years ago used urea solutions in the dressing of wounds with excellent results, that Millar used it later in suppressing the foul odors of sloughing cancer, and that Folger and Foshay used it in treating infected wounds of various sorts.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

RESIDUAL SIGNS OF CORONARY OCCLUSION

To the Editor:—I was requested to examine an applicant for an insurance policy, January 19. The applicant is 46 years old and is the owner of a wholesale grocery establishment, where he is busily engaged the entire day. His general appearance, actions and behavior did not indicate any possible ailment. He was alert, quick in his actions, stated that he had never been treated for any ailment, and also stated that he never received compensaton for any physical disability. His weight is 162 pounds (73.5 Kg.), height 5 feet 4 inches (163 cm.), blood pressure 124 systolic, 78 diastolic and pulse rate 74 per minute, the pulse being regular and of good quality. The heart and lungs showed no apparent pathologic changes. The urine examination was negative save for the Fehling test being slightly reduced. I therefore recommended the acceptance of the risk. Shortly afterward I received a letter from the home office stating that the applicant had been rejected for the reason that he was treated for coronary occlusion in February 1937, as corroborated by electrocardiogram; he also received compensation for this disability. Will you kindly inform me whether it is possible to find any physical signs or symptoms of coronary occlusion a year after it has occurred? Are there any such signs left?

M.D., Connecticut.

ANSWER.—In many cases there are signs and symptoms that will point to a coronary occlusion a year before, whereas in other cases there are none. The occlusion of a large artery with an extensive infarction of the heart muscle that later causes scarring with a thinning and bulging of the wall of the ventricle may lead to results that are clearly in evidence a year later. Increase in the size of the heart, alterations of its rate and rhythm, dyspnea and other evidences of cardiac weakness, and anginal distress on exertion, together with significant electrocardiographic changes, may be present. Mild attacks due to occlusion of a small artery may be so nearly recovered from that no symptom or sign of the accident can be detected a year later. Even the electrocardiogram may seem normal or show changes so slight that they can be passed as meaningless. Had the applicant not lied regarding his health history of the past year the examination would perhaps have been more intensively centered on the heart and might have included an electrocardiogram. Possibly in this way some suspicion of residual damage might have been aroused. Yet no such evidence might have been found.

PELLAGRA

To the Editor:—A patient with pellagra of moderate severity has a cutaneous disturbance involving the backs of both hands, two fingers of each hand, the legs below the knees and the chest, throat and chin. The condition on the legs, chin and chest has cleared up, and on the hands except for a small area. The treatment used was a potassium permanganate solution for the skin, and liver extract for the anemia. The red blood count is now 4,200,000, white count 6,300, hemoglobin 7,590. Sedatives are still necessary to induce sleep and relieve the itching of the hands. The patient has a nurse and I am pushing the pellagra diet. What else is there to do for the itching and mental state? What outline do you offer for general treatment?

RUSSELL L. HODGE, M.D., North Kansas City, Mo.

ANSWER.—The general treatment of pellagra is to keep the patient in bed until convalescence is well established. Constant nursing care will conserve the patient's strength and will assure one that specific and therapeutic materials have been given. It is essential that a pellagrin eat a well balanced diet of 4,500 calories or more each day. Unless there is vomiting or diarrhea, it is desirable that this diet be administered in the form of solid foods. Diets suitable for patients with pellagra were discussed by Spies, Chinn and McLester in THE JOURNAL, March 13, 1937, page 853. It is also desirable that the patient receive about 6 ounces (175 cc.) of dried powdered brewers' yeast daily. It is best tolerated when given in doses of from 20 to 30 Gm. in 200 cc. of milk. If the patient still has lesions of the mucous membranes, nicotinic acid may be given in five doses of 100 mg. each per day. It is perhaps advisable to discontinue sedatives for a short period even though the patient does not sleep well, since the mental symptoms of pellagra often overlap those of drug intoxication and apparently patients with pellagra are more susceptible to some of these drugs than are normal persons. The itching and burning sensations associated with pellagra usually disappear promptly after definite recovery has set in. If these symptoms linger, another cause for them should be sought. Symptomatically, they are often relieved by a mixture of 1 per cent phenol in menthol, applied locally.

DOSAGE OF DESICCATED THYROID

To the Editor:—Can any child take 9 grains (0.6 Gm.) of desiccated thyroid daily for more than one year and gain weight and not have hypothyroidism? What are the maximum doses of thyroid known to be given over long periods, and at what ages?

M.D., Elmhurst, L. I.

ANSWER.—The question of hypothyroidism in a particular case can be settled beyond doubt by observing any change in the clinical condition of the patient and the basal metabolic rate after omitting thyroid for from four to six weeks. Six-tenths Gm. of desiccated thyroid daily is an unusually large dose if the thyroid is standardized according to U. S. P. specifications. Marked variations in dosage of thyroid may occur in different persons and rarely in the same person at different times. Most patients with myxedema sustain a normal basal metabolic rate by 0.13 Gm. or less of U. S. P. desiccated thyroid daily. Gain in weight while taking 0.6 Gm. of U. S. P. thyroid daily would suggest that much of the thyroid taken was not absorbed and, if anything, would argue against the presence of true hypothyroidism, or myxedema. Some patients, more particularly those with pituitary disease, anorexia nervosa or similar conditions, may need larger doses to maintain a metabolic rate at or near the standard average. Thyroid dosage should, in each and every instance, be determined for the individual patient by his or her response to constant dosages. There is no constant variation of the dosage with different ages.

ALLERGY OF MOUTH TO FOODS

To the Editor:—A woman, aged 18, has had a sore, ulcerated roof of the mouth on two occasions in the last two months. She is in excellent physical condition. Her tonsils are out, and her teeth and gums are apparently healthy. Her two attacks have been ushered in by a hivelike condition of her face, characterized by swelling, itching and a sense of not feeling well. There is no fever. In about two days the face condition clears up (it has always been in the same places) and the mouth condition, which has not been severe but only sore, becomes aggravated, then ulcerated. At no other place in the oral cavity is there pathologic disturbance. Menstruation has no effect on the condition. I have used sodium perborate and other oral antiseptics without any relief. After ten days it goes away. I have blamed some allergic factor for the condition, but what would it be?

M.D., Wisconsin.

ANSWER.—The condition described is most likely an allergic manifestation. It is apparently an urticarial type of reaction on the skin associated with a canker sore type of lesion in the mucous membranes of the mouth. Recurring canker sores caused by allergic factors have been described a number of times and are apparently not rare in allergic practice. Almost always these lesions are caused by an allergy to foods. Among some of the common foods which have been incriminated in this type of allergy have been chocolate, wheat and milk. If possible, this patient should be tested for food allergy. If such means are not available, an elimination diet should be tried. It is also possible that, by careful observation and keeping a record of foods preceding the onset of these attacks, the cause may be identified in this manner.

DISSOLVING TISSUES FROM SKELETON—BLEACHING BONES—ARTICULATION OF SKELETON

To the Editor:—Will you kindly advise me of a suitable, fairly simple technic for dissolving some remaining tissue from an old skeleton and a bleaching agent for the bones? If there are available any instructions for the articulation of a skeleton, showing the best method of placing the wires, this also would be appreciated.

R. L. MANSELL, M.D., Medina, Ohio.

ANSWER.—The tissues adherent to an old skeleton can be removed first by careful dissection. The remaining ends of muscles and tendons can be removed by boiling the parts in sodium hydroxide solution (from 4 to 10 per cent strength; the stronger solution should be used only if it is the intention to disarticulate the bones and to remove the cartilages covering the ends). In either case the bones should be carefully watched and removed every ten minutes. The remnants of tissues should then be cut or scraped off and the bones brushed with a stiff brush and then returned to the solution; this process is to be repeated until the bones are as clean as desired. Some of the smaller bones should be taken out earlier than the large ones. The cord and the dura mater may be removed from the vertebral canal without disarticulating the vertebrae by loosening the dura at each end of the vertebral canal. The intervertebral

disks will withstand boiling for some time and may be left in place if so desired and the vertebral column preserved in one piece.

When the bones are sufficiently clean, the soda is poured off and the bones are washed in hot water. Any excess of grease is removed by soaking in gasoline, and the bones may then be bleached by immersion in 10 per cent hydrogen peroxide. Chlorinated lime is sometimes used for this purpose, the bones being boiled in it for a quarter of an hour; this bleaching agent, however, is apt to injure the bone, making the outer surfaces scaly and soft. Finally, the bones are dried in the open air.

If desired, they may be varnished over with a varnish made of Canada balsam, dissolved to the desired thickness in a mixture of equal parts of xylene and alcohol.

The wires and metal parts required for the articulation of the skeleton may be obtained from some of the companies which deal in skeletons, including the Denoyer-Geppert Company, 5235 North Ravenswood Avenue, Chicago.

BRAIN INJURY OR POST-TRAUMATIC NEUROSIS

To the Editor:—In July 1935 an 18 year old girl, a housemaid, was struck by an automobile and thrown 40 or 45 feet. She suffered contusions of the left parietal region, right knee and right arm. There was also a deep laceration about 1½ inches long on the right arm. Three days after the accident she noticed weakness in her left arm and leg. She was told by her attending physician not to worry about the weakness. I first examined her in March 1936, when she complained of weakness in the right arm and leg and a tingling sensation present only for from two to four minutes every five to seven days. The weakness of the hand had been progressive and was then so severe that she could write only half of an ordinary letter page without stopping to rest. Physical examination at this time showed the blood pressure in the right arm 140/100 and in the left arm 120/100. The reflexes were equal and active. Sensation to touch, heat, cold and joint position was normal. Coordination was good except that after slight exercise of the right hand definite weakness accompanied by moderate incoordination would appear. In May 1936 the tingling sensation was less severe. The blood pressure in the right arm was 128/100 and in the left arm 120/100. The weakness continued. In July 1936 the blood pressure in the right arm was 130/86 and in the left arm 120/80; weakness continued. In August 1937 she complained of weakness in the right forearm and hand and in the right leg and foot. Muscular strength was good above the knee and elbow. There have been no attacks of tingling for six months. Reflexes and the sensorium continue to be normal. Is there any anatomic basis that will explain these symptoms? If not, what other tests should be done before making the diagnosis of neurosis? Could these symptoms possibly be the precursors of jacksonian epilepsy?

M.D., Illinois.

ANSWER.—Before making a diagnosis of post-traumatic neurosis it would be wise to make an encephalogram to rule out brain injury. Only if an encephalogram, skull roentgenograms, spinal fluid pressure studies and repeated careful neurologic examinations give normal results could one consider the diagnosis of neurosis. The tingling sensations described might well be a sensory jacksonian discharge.

DIPLOPIA AND PTOSIS

To the Editor:—A Negro, aged 27, woke one morning with diplopia. This condition has persisted unchanged for one month. There is no headache, vomiting or dizziness. Examination shows ptosis of the right eyelid and almost complete paralysis of the superior, inferior and internal recti of the right eye. The left eye is normal. The pupils are equal and react to light and in accommodation. The fundi and visual fields are normal. Complete neurologic examination reveals no other abnormalities. Repeated Kahn tests are negative. Spinal tap is normal. An incomplete peripheral lesion of the oculomotor nerve was diagnosed. Could you help me as to other possible locations of the lesion and as to possible underlying etiology?

M.D., New York.

ANSWER.—It is not stated whether or not the right pupil was larger than the left. From the neurologic information given the probabilities are that the lesion is in the region of the nucleus of the third nerve rather than in the nerve branches themselves, and the cause is probably a localized encephalitis.

RADIUM AND INCIPIENT CATARACT

To the Editor:—A patient has been advised that the use of "radium on the lids" of her eyes would be a cure for incipient cataract. Is there information to be had regarding this?

LOUIS L. SHERMAN, M.D., Oakland, Calif.

ANSWER.—The use of radium as a cure for incipient cataract has been tried off and on during the past twenty-five years but has been entirely abandoned because of the dangers. It is well known that the external application of radium about the orbit can cause the production of lens opacities of the posterior portion of the lens in a characteristic form (Meesmann: Kurzes Handbuch der Ophthalmologie, vol. 5). There is no valid reason to believe that radium applied to the eyelids can cause a disappearance of lens opacities.

Headed by Dr. Allen Greenwood of Boston, a committee of the American Academy of Ophthalmology and Oto-Laryngology reported at the 1933 meeting (*Tr. Am. Acad. Ophth. & Oto-Laryng.*, 1933, p. 478) on its investigation of the medical treatment of incipient cataract. The gist of the report was "We fail to find that there is scientific proof that the medicinal treatment of lenticular opacities will cause a restoration of the normal transparency of the lens."

ETIOLOGY OF ROSACEA

To the Editor:—What is the etiology of rosacea?

J. S. BEALLE, M.D., Holt, Ala.

ANSWER.—Rosacea occurs more often in women than in men and usually after 30 years of age, though rarely it appears earlier. The more severe forms usually are found in men. It may be produced by a number of causes acting individually or together. Undoubtedly there is a hereditary predisposition. Alcohol is popularly considered to induce rosacea, but it actually does so in only a minority of cases. Alcohol, very warm foods and highly spiced foods will aggravate a rosacea already present. Gastro-intestinal disturbances may bear a relation. Both hypoacidity and hyperacidity have been found in gastric analyses. Constipation is frequently mentioned by women. Cirrhosis of the liver may also be a factor. Many patients have organic or functional disturbances of the ovaries and uterus. Among the locally acting agents, Demodex folliculorum, an organism that lives in the hair follicles, and Sabouraud's bacillus of seborrhea have been incriminated. Infections within the nose, such as chronic folliculitis and obstructions, may be causative. Wind and weather probably can induce it and certainly make an existing rosacea worse.

PRESERVATION OR STERILIZATION OF CARTILAGE FOR GRAFTING

To the Editor:—Please let me know what chemicals are suitable for sterilizing cartilage to be used in isoplastic grafting.

JOHN F. FORD, M.D., New York.

ANSWER.—The question does not make clear whether it is wished to sterilize cartilage that has become contaminated or whether it is the desire to preserve sterile cartilage for later transplantation. In general, cartilage which is to be used as a transplant is removed under rigidly aseptic conditions and if the transplantation is done immediately the use of an antiseptic is neither necessary nor desirable. Occasionally conditions may arise in which it is desirable to preserve an excised cartilage for later transplantation. When the delay is to be of only a few hours, immersion of the sterile cartilage in sterile physiologic solution of sodium chloride is satisfactory. For longer preservation, immersion in an antiseptic solution, such as a 10 per cent solution of tincture of metaphen, has been recommended. There are no data at hand, however, which would enable one to state what chemical is to be preferred.

If the excised cartilage has been contaminated, the use of an antiseptic solution for sterilization should not be depended on under any circumstances.

USE OF NARCOTICS IN PARALYSIS AGITANS AND CANCER

To the Editor:—A few months ago I was called to see a patient with advanced paralysis agitans complaining of severe muscle cramps. The usual remedies for this disease have been used to the extent that they are no longer effective. In order to give him some rest at night his mother begged me to give him a narcotic. The results of the narcotic were so gratifying that he has taken it during the daytime also. Is it safe to prescribe morphine for this patient and to what extent can one prescribe it and still abide by the narcotic law? How much morphine does the law allow one to prescribe for a patient with cancer?

M.D., Illinois.

ANSWER.—No person is immune to narcotic addiction. Morphine administered to any hundred persons will make a hundred addicts irrespective of the pathologic necessity. One should avoid repeating the dose of an opiate when great relief is given or when more than an anodyne effect is secured, especially in neurotic patients.

In an inoperable carcinoma there is no narcotic question involved; the patient should receive enough morphine or other opiate to control the pain. As a rule it is much better to administer opiates by mouth and avoid the quick hypodermic narcotic relief sensation. Where narcotics in chronic incurable cases are a necessity it is much better to give the total twenty-four hour amount to be used in equal divided doses and administer them two or three times a day at regular intervals. The narcotic law says nothing about the amount one can prescribe or give any one patient.

REMOVAL OF CONJUNCTIVAL SILVER STAIN—HAIR DYES AND OPTIC ATROPHY

To the Editor:—Can anything be done to remove a conjunctival stain due to mild protein silver (argyria)? Is there any basis for the repeated statement that hair dyes may be the cause of glaucoma or atrophy of the optic nerve?

M. SHELDON LORD, M.D., Schenectady, N. Y.

ANSWER.—Conjunctival argyria can be removed by the method of Stillians and Lawless, which is applied to the staining of the skin. A mixture of equal parts of 6 per cent sodium thiosulfate and 1 per cent potassium ferricyanide is injected subconjunctivally through a fine needle, which must be made of platinum. The eye may be cocainized in the usual way or procaine hydrochloride may be injected previously. Not more than 0.4 cc. is usually injected at a time, this being distributed under the bulbar conjunctiva in the stained area. The procedure can be repeated as often as necessary to cover the exposed portion. It is only necessary to treat the part of the bulbar conjunctiva that is exposed when the eye is opened. The inside of the lids is usually left alone.

There seems to be little basis for the belief that hair dyes are the cause of glaucoma or optic atrophy, although they may cause damage to the lids and cornea. Hair remover containing thallium does cause optic atrophy when taken internally or absorbed through the skin in large quantities.

DINITROCHLOROBENZENE AND CATARACTS

To the Editor:—Is there any evidence attributing opacities of the crystalline lens to general poisoning by exposure to dinitrochlorobenzene?

HOWARD C. KNAPP, M.D., East St. Louis, Ill.

ANSWER.—The best general studies on dinitrochlorobenzene have been made by the Russians Gorkin and Kagan at the Ukrainian Institute of Pathology and Hygiene of Work. This investigation has been extended a long review in the *Journal of Industrial Hygiene and Toxicology* (**18**:156, 1936). The results of the investigation closely associate this substance with dinitrophenol as to toxic properties, although the two substances are chemically dissimilar except that each represents a nitro compound of the benzene ring. The recent extensive use of dinitrophenol for the treatment of obesity was followed, beginning in 1934, by frequent occurrence of cataracts. The incidence of cataracts was as high as 1 per cent in some series. Because of similarity in the general states produced by these two chemicals, cataracts from the action of dinitrochlorobenzene is a fair expectancy, although no precise case records have been found.

EXCESSIVE LIBIDO IN WOMAN

To the Editor:—A woman, aged 30, is greatly troubled with excessive libido. She had no sex trouble till the birth of her first baby five years ago. During her two subsequent pregnancies she was indifferent sexually, but excessive libido returned following each delivery. Would you suggest that antuitrin-S or theelin or both are indicated?

M.D., Michigan.

ANSWER.—Neither of the preparations mentioned nor similar ones have any effect on libido, as it is not ovarian in origin. Even removal of both ovaries will have no effect. The seat of the trouble is in the brain and not in the sexual apparatus. For the severer types of the condition, called nymphomania, every possible therapeutic method, including castration, roentgen therapy of the ovaries, hypnotism and even marriage to a male suffering from a similar condition (satyriasis), has been tried with absolutely no effect. The milder cases may be treated with bromides or similar sedatives. Opiates must be avoided. It is important to determine whether the condition is induced or exaggerated by the practice of withdrawal on the part of a husband or even impotence, partial or complete, of the husband.

LEUKOPENIC INDEX

To the Editor:—I should like to add the result of my study on the subject of the leukopenic index to your answer to the questions from M.D., Arkansas, in THE JOURNAL, Dec. 11, 1937. The blood count after ingestion of 8 ounces of milk following a fifteen hour fast should not be influenced at all if the patient is normal. I feel, too, that no definite rule can be made concerning the behavior of the leukocytes following ingestion of any food. From the point of view of clinical medicine, any food that causes distress should be removed from the patient's diet; this view, however, cannot be corroborated by a laboratory finding of either leukocytosis or leukopenia. For detailed comment and experience on this subject I would refer the physician not only to the works you have already mentioned but also to my article in the July 3, 1937, issue of THE JOURNAL, entitled "Leukocyte Behavior During Gastric Analysis."

CHARLES-FRANCIS LONG, M.D., Philadelphia.

Medical Examinations and Licensure

COMING EXAMINATIONS

STATE AND TERRITORIAL BOARDS

ALABAMA: Montgomery, June 28. Sec., Dr. J. N. Baker, 519 Dexter Ave., Montgomery.

ARIZONA: *Basic Science.* Tucson, March 15. Sec., Dr. Robert L. Nugent, Science Hall, University of Arizona, Tucson. *Medical.* Phoenix, April 5-6. Sec., Dr. J. H. Patterson, 826 Security Bldg., Phoenix.

ARKANSAS: *Medical (Regular).* Little Rock, June 21-22. Sec., State Medical Board of the Arkansas Medical Society, Dr. L. J. Kosminsky, Texarkana. *Medical (Eclectic).* Little Rock, June 21. Sec., Dr. Clarence H. Young, 1415 Main St., Little Rock.

CALIFORNIA: *Reciprocity.* San Francisco, May 11, Los Angeles, July 11, San Francisco, Sept. 14, and Los Angeles, Nov. 16. *Written examinations.* Los Angeles, March 7-10, San Francisco, June 27-30, Los Angeles, July 11-14, and Sacramento, Oct. 17-20. Sec., Dr. Charles B. Pinkham, 420 State Office Bldg., Sacramento.

COLORADO: Denver, April 6-8. Sec., Dr. Harvey W. Snyder, 831 Republic Bldg., Denver.

CONNECTICUT: *Medical (Regular).* Hartford, March 8-9. *Endorsement.* Hartford, March 22. Sec., Dr. Thomas P. Murdock, 147 W. Main St., Meriden. *Medical (Homeopathic).* Derby, March 8. Sec., Dr. Joseph H. Evans, 1488 Chapel St., New Haven.

DELAWARE: Dover, July 12-14. Sec., Medical Council of Delaware, Dr. Joseph S. McDaniel, 229 S. State St., Dover.

DISTRICT OF COLUMBIA: *Basic Science.* Washington, June 27-28. *Medical.* Washington, July 11-12. Asst. Sec., Commission on Licensure, Mr. Paul Foley, 203 District Bldg., Washington.

FLORIDA: Jacksonville, June 13-14. Sec., Dr. William M. Rowlett, Box 786, Tampa.

GEORGIA: Atlanta, June. Joint Sec., State Examining Boards, Mr. R. C. Coleman, 111 State Capitol, Atlanta.

HAWAII: Honolulu, April 11-14. Sec., Dr. James A. Morgan, 48 Alexander Young Bldg., Honolulu.

IDAHO: Boise, April 5-6. Commissioner of Law Enforcement, Hon. J. L. Balderston, 205 State Capitol Bldg., Boise.

ILLINOIS: Chicago, April 5-7, June 28-July 1, and Oct. 18-20. Superintendent of Registration, Department of Registration and Education, Mr. Homer J. Byrd, Springfield.

INDIANA: Indianapolis, June 21-23. Sec., Board of Medical Registration and Examination, Dr. J. W. Bowers, 301 State House, Indianapolis.

KANSAS: Kansas City, June 7-8. Sec., Board of Medical Registration and Examination, Dr. J. F. Hassig, 905 N. 7th St., Kansas City.

KENTUCKY: Louisville, June 8-10. Sec., State Board of Health, Dr. A. T. McCormack, 620 S. 3rd St., Louisville.

MAINE: Portland, March 8-9. Sec., Board of Registration of Medicine, Dr. Adam P. Leighton, 192 State Street, Portland.

MARYLAND: *Medical (Regular).* Baltimore, June 21-24. Sec., Dr. John T. O'Mara, 1215 Cathedral St., Baltimore. *Medical (Homeopathic).* Baltimore, June 21-22. Sec., Dr. John A. Evans, 612 W. 40th St., Baltimore.

MASSACHUSETTS: Boston, March 8-10. Sec., Board of Registration in Medicine, Dr. Stephen Rushmore, 413-F State House, Boston.

MICHIGAN: Ann Arbor and Detroit, June 15-17. Sec., Board of Registration in Medicine, Dr. J. Earl McIntyre, 202-3-4 Hollister Bldg., Lansing.

MINNESOTA: *Basic Science.* Minneapolis, April 5-6. Sec., Dr. J. Charnley McKinley, 126 Millard Hall, University of Minnesota, Minneapolis. *Medical.* Minneapolis, April 19-21. Sec., Dr. Julian F. Du Bois, 350 St. Peter St., St. Paul.

MISSISSIPPI: Jackson, June. Asst. Sec., State Board of Health, Dr. R. N. Whitfield, Jackson.

MONTANA: Helena, April 5-6. Sec., Dr. S. A. Cooney, 205 Power Block, Helena.

NEBRASKA: *Basic Science.* Omaha, May 3-4. Dir., Bureau of Examining Boards, Mrs. Clark Perkins, State House, Lincoln.

NEW HAMPSHIRE: Concord, March 10-11. Sec., Board of Registration in Medicine, Dr. Fred E. Clow, State House, Concord.

NEW JERSEY: Trenton, June 21-22. Sec., Dr. James J. McGuire, 28 W. State St., Trenton.

NEW MEXICO: Santa Fe, April 11-12. Sec., Dr. Le Grand Ward, 135 Sena Plaza, Santa Fe.

NEW YORK: Albany, Buffalo, New York and Syracuse, June 27-30 and Sept. 19-22. Chief, Professional Examinations Bureau, Mr. Herbert J. Hamilton, 315 Education Bldg., Albany.

NORTH CAROLINA: Raleigh, June 13. Sec., Dr. B. J. Lawrence, 503 Professional Bldg., Raleigh.

NORTH DAKOTA: Grand Forks, July 5-8. Sec., Dr. G. M. Williamson, 4½ S. 3rd St., Grand Forks.

OKLAHOMA: *Basic Science.* Oklahoma City, May 4. Sec. of State, Hon. Frank C. Carter, State Capitol Bldg., Oklahoma City. *Medical.* Oklahoma City, June 8-9. Sec., Dr. James D. Osborn Jr., Frederick.

OREGON: *Basic Science.* Portland, March 19, Corvallis, July 16, and Portland, Nov. 19. Sec., State Board of Higher Education, Mr. Charles D. Byrne, University of Oregon, Eugene. *Medical.* Portland, April 6. Sec., Dr. Joseph F. Wood, 509 Selling Bldg., Portland.

PENNSYLVANIA: Philadelphia and Pittsburgh, July. Sec., Board of Medical Education and Licensure, Dr. James A. Newpher, 400 Education Bldg., Harrisburg.

RHODE ISLAND: Providence, April 7-8. Chief, Division of Examiners, Mr. Robert D. Wholey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: Columbia, June 28. Sec., Dr. A. Earle Boozer, 505 Saluda Ave., Columbia.

SOUTH DAKOTA: July 19-20. Director of Medical Licensure, Dr. B. A. Dyar, State Board of Health, Pierre.

TEXAS: San Antonio, June 20-22. Sec., Dr. T. J. Crowe, 918 Mercantile Bldg., Dallas.

VIRGINIA: Richmond, June 22-24. Sec., Dr. J. W. Preston, 30½ Franklin Road, Roanoke.

WEST VIRGINIA: Huntington, March 21-23. Sec., Public Health Council, Dr. Arthur E. McClue, State Capitol, Charleston.

WISCONSIN: *Basic Science.* Madison, April 2. Sec., Prof. Robert N. Bauer, 3414 W. Wisconsin Ave., Milwaukee. *Medical.* Milwaukee, June 28-July 1. Sec., Dr. Henry J. Gramling, 2203 S. Layton Blvd., Milwaukee.

NATIONAL BOARD OF MEDICAL EXAMINERS SPECIAL BOARDS

Examinations of the *National Board of Medical Examiners* and *Special Boards* were published in THE JOURNAL, February 26, page 679.

Pennsylvania Reciprocity and Endorsement Report

Dr. James A. Newpher, secretary, Board of Medical Education and Licensure, reports 8 physicians licensed by reciprocity and one physician licensed by endorsement from Nov. 4 through Dec. 3, 1937. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
University of California Medical School		(1933)	California
George Washington University School of Medicine		(1932)	Dist. Colum.
Howard University College of Medicine		(1932)	Maryland
University of Nebraska College of Medicine		(1932)	Nebraska
Western Reserve University School of Medicine		(1927)	Ohio
University of Pennsylvania School of Medicine		(1931)	N. Carolina
Woman's Medical College of Pennsylvania		(1926)	New York
Medical College of Virginia		(1914)	Virginia

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
Boston University School of Medicine		(1932)	N. B. M. Ex.

Missouri October Examination

Dr. Herman S. Gove, director of medical licensure, reports the written examination held in Kansas City, Oct. 20-22, 1937. Twenty-five candidates were examined, 24 of whom passed and one failed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
University of Arkansas School of Medicine		(1937)	76.9
Howard University College of Medicine		(1935) 82.9, (1936)	89.1
Northwestern University Medical School		(1935) 86.6, (1937)	85.2*
Rush Medical College		(1937)	85.3
School of Medicine of the Division of the Biological Sciences		(1937)	82.2
University of Illinois College of Medicine		(1937)	86.9*
University of Kansas School of Medicine		(1937)	81.5, 86.3, 87.1
University of Louisville School of Medicine		(1937)	85.3
St. Louis University School of Medicine		(1936) (1937)	84.9, 79.2, 83.4, 85.3
Washington University School of Medicine		(1937)	79.7, 85.1
New York University College of Medicine		(1937)	86.5
Jefferson Medical College of Philadelphia		(1934)	82.2
University of Pennsylvania School of Medicine		(1937)	88.4, 89.7
Medical College of Virginia		(1937)	83.3
University of Wisconsin Medical School		(1936)	80.9

School	FAILED	Year Grad.
Meharry Medical College		(1935)

Forty-four physicians were licensed by reciprocity and six physicians were licensed by endorsement from October 19 through December 22. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
University of Arkansas School of Medicine		(1931) (1935)	Oklahoma, Arkansas
Northwestern University Medical School		(1904), (1929)	Illinois
Rush Medical College		(1901)	Nebraska
University of Illinois College of Medicine		(1937, 3)	Illinois
Indiana University School of Medicine		(1936)	Indiana
Kansas Medical College, Kansas		(1913)	Kansas
University of Kansas School of Medicine		(1931), (1934, 3), (1935), (1936, 4)	Kansas
University of Louisville School of Medicine		(1936, 2)	Kentucky
University of Michigan Homeopathic Medical School		(1890)	Kansas
St. Louis College of Physicians and Surgeons		(1920)	Colorado
St. Louis University School of Medicine		(1928) (1936)	Kansas, New York
Washington University School of Medicine		(1910)	Nebraska
University of Nebraska College of Medicine		(1920) (1933), (1934)	Iowa, Nebraska
Columbia Univ. College of Physicians and Surgeons		(1923)	New York
University of Buffalo School of Medicine		(1929)	New York
Hahnemann Med. College and Hospital of Philadelphia		(1936)	Maryland
Lincoln Memorial University Medical Department, Tennessee		(1916)	Kentucky
Meharry Medical College		(1933), (1934), (1936, 4)	Tennessee
University of Tennessee College of Medicine		(1934), (1935, 2), (1936)	Tennessee
University of Texas School of Medicine		(1936)	Texas

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
College of Medical Evangelists		(1937)	N. B. M. Ex.
Yale University School of Medicine		(1936)	N. B. M. Ex.
Northwestern University Medical School		(1936)	N. B. M. Ex.
St. Louis University School of Medicine		(1936)	N. B. M. Ex.
Washington University School of Medicine		(1930), (1936)	N. B. M. Ex.

* This applicant has completed the medical course and will receive the M.D. degree on completion of internship. License has not been issued.

Book Notices

Crippled Children: Their Treatment and Orthopedic Nursing. By Earl D. McBride, B.S., M.D., F.A.C.S., Assistant Professor of Orthopedic Surgery, University of Oklahoma School of Medicine, Oklahoma City. In collaboration with Winifred R. Sink, A.B., R.N., Educational Director, Grace Hospital School of Nursing, Detroit, Michigan. Second edition. Cloth. Price, $3.50. Pp. 379, with 195 illustrations. St. Louis: C. V. Mosby Company, 1937.

There are few satisfactory books dealing with the principle of orthopedic nursing, but this volume is one of them. The title indicates that the authors' primary interest was the nursing profession, but this book would be helpful and instructive as well as interesting reading for all who have the care and responsibility of crippled children, including medical social service workers, members of boards of managers of crippled children's hospitals, and the socially conscious lay public. The book is arranged in an orderly fashion. It begins with an introduction to the field of orthopedic surgery and a brief history of the development of this specialty and continues with a description of the type of work that is done, the facilities that are available and a discussion of the problem as a whole. The first nine chapters are largely confined to questions of special interest to orthopedic nurses. There is an adequate description of physical therapy and of braces and their care. The remainder of the book is concerned with brief descriptions of most of the conditions that cause crippling. It is possible that more is said about medical and surgical treatment than is entirely appropriate in a textbook of this type. However, at the end of each chapter the points of special nursing interest are listed in a 1 2 3 order. This should make the book exceedingly helpful to nurses who have not had adequate apprenticeships in hospitals where large numbers of orthopedic cases are cared for. If every general practitioner in the country would take the time to read this book, the value of his service as medical adviser to the families in the community in which he lives would be greatly increased. There would be less tendency on the part of some doctors to unwittingly mislead parents by telling them that their child would outgrow a limp or deformity which could be cured or improved only by application of modern orthopedic principles.

Nurses Handbook of Obstetrics. By Louise Zabriskie, R.N., Field Director Maternity Center Association, New York City. Fifth edition. Cloth. Price, $3. Pp. 724, with 384 illustrations. New York & London: J. B. Lippincott Company, 1937.

Miss Zabriskie has incorporated in this revised edition the newer phases of obstetric nursing. The author is eminently fitted by experience, accomplishments and sympathetic insight to write a nurses' handbook of obstetrics. She has been ably assisted by collaborators chosen for distinction in their special fields. Material selected from the leading and progressive maternity centers of the country makes the book a source of valuable information. The technics and procedures demonstrated are practical and reliable. Especially noteworthy are the many original photographs, anatomic drawings, illustrations, roentgenograms, graphs and vital statistics, which clarify the text and eliminate lengthy descriptions. Related subjects are grouped together in units, giving coherence and continuity to the whole and making it especially effective for teaching purposes. The brief orientation introducing each unit familiarizes the student with the aim and content of the course. The basic facts underlying the practice of good obstetrics are forcibly and clearly presented. Beginning with the fundamental chapters on anatomy and physiology, the normal woman is brought through her pregnancy, labor and the puerperium with special emphasis on the prevention of obstetric complications. There is a comprehensive and authoritative discussion of the development and needs of the new-born infant and the hazards to which it is particularly susceptible at this critical period of its life. The subject of diet is considered in detail and its important effect on mother and baby during pregnancy and lactation. One of the valuable features of the book is the interesting and thought provoking article on the emotional factors of pregnancy and the role conditioning has in the behavior patterns of the infant. The busy practitioner will be able to utilize many of the worthwhile suggestions on home delivery and care. In the last

unit the ecbolics, analgesics and anesthetics now in vogue are discussed. The important place x-rays are assuming in obstetric diagnosis and an excellent history of obstetrics are included. The author has discussed the most direct and telling methods used today to prevent deaths from toxemia, infection and accidents due to faulty diagnoses and mishandling. The book is not a mass of theory on controversial subjects but of factual knowledge and perfected methods that can be put to practical and effective use.

The Therapeutic Problem in Bowel Obstructions: A Physiological and Clinical Consideration. By Owen H. Wangensteen, B.A., M.D., Ph.D., Professor of Surgery of the University of Minnesota. Cloth. Price, $6. Pp. 360, with 90 illustrations. Springfield, Illinois, & Baltimore: Charles C. Thomas, 1937.

Recognition has already been extended this monograph, the first section of which has been awarded the Samuel D. Gross prize for 1935. The author has appended two more sections of about equal length, which go into greater detail than the prize winning first portion. Essentially based on direct physiologic evidence obtained in the experimental laboratory and coupled with data obtained clinically, this piece of work is a fundamental contribution to surgery. While the first part deals only with laboratory observations and therapeutic applications in a general way, the latter portions are directed to specific clinical conditions. The author is a well known exponent of decompression of the bowel by inlying duodenal suction. He explains his rationale for this procedure as well as the method of application. A firm proponent of the noxious effects of mechanical influences as against the older theory of absorbed toxins from the obstructed intestine, he presents his case well. Stress is laid on diagnosis, and x-ray examination is featured. All in all this is a profitable source for any surgeon called on to deal with the diseases of the abdomen.

Crime, Crooks and Cops. By August Vollmer and Alfred E. Parker. Cloth. Price, $2. Pp. 260. New York & London: Funk & Wagnalls Company, 1937.

August Vollmer has a reputation gained as chief of police of Los Angeles and as professor of police administration at the University of California, which makes his contribution to the science of crime detection well worth while. It is of special interest to the medical profession because doctors frequently are concerned with examinations of the blood and hair, finger printing, personal identification and other aspects of this subject. The book here reviewed is based on actual cases, including among other items the use of the lie detector in several investigations and a consideration of its standing in court. The concluding chapters are concerned with the qualifications for police officers, which again are questions that might intimately concern members of the medical profession.

L'exploration fonctionnelle du pancréas interne. A l'état normal, dans le diabète sucré, dans le diabète du jeûne, et après insulinisation prolongée. Étude expérimentale et clinique. Par le Dr. René Saric. Paper. Pp. 238, with illustrations. Bordeaux: Librairie Delmas, [n. d.].

This is a monographic report of extensive investigation of the internal function of the pancreas by means of blood sugar time curves. The investigation covered tests made on normal dogs, dogs with complete and partial pancreatectomy and dogs with the pancreas intact, which had been treated for prolonged periods with insulin. Clinical diabetes of various types was similarly investigated before and after fasting, and before and in the course of treatment with insulin. Microscopic examination of the pancreas of animals that had received insulin for several months revealed hyperplasia of the islands of Langerhans. Significant conclusions are that hyperglycemia is the physiologic excitant of the insular function, but overloading with sugar is depressing to the islands, the more so if they already are injured; that treatment with insulin by a splinting effect causes normally an increase of insular tissue and increased amount of stored insulin; that a regimen rich in carbohydrate, without insulin, brings on fatal aggravation of pancreatic injuries, while excessive treatment with insulin and permanent relative hypoglycemia diminishes the activity of the insular tissue. The happy mean which ought to represent ideal treatment should be sufficiently intense insulinization to protect the pancreas from being overloaded by the requirement of insulin resulting from food taking, and a sufficient allowance of carbohydrate in the diet to maintain normal insular function. The monograph will appeal to physicians and experimentalists interested in the theory of diabetes.

The Neurotic Personality of Our Time. By Dr. Karen Horney. Cloth. Price, $3. Pp. 299. New York: W. W. Norton & Company, Inc., 1937.

The interested layman as well as the physician will find here a form of psychologic analysis built on the freudian contribution but not essentially the same. Dr. Horney recognizes the great influence of our environment and culture on our points of view and on our mentality. Perhaps the most significant of the chapters in the work is the consideration given to the part played by sexuality in the neurotic need for affection. Certainly Dr. Horney reveals in this book a profound understanding of the nature of the neurosis and it is her conclusion that the person who is likely to become neurotic is the one who has experienced the culturally determined difficulties in an accentuated form, mostly through the medium of childhood experiences, and who has consequently been unable to solve them or has solved them only at great cost to his personality.

Flying Vistas: The Human Being, as Seen Through the Eyes of the Flight Surgeon. By Isaac H. Jones, M.A., M.D., Medical Examiner, Bureau of Air Commerce, United States Department of Commerce. Cloth. Price, $2. Pp. 255, with illustrations. Philadelphia & London: J. B. Lippincott Company, 1937.

The relation and importance of physical fitness to aviation are aptly portrayed by the author in nontechnical language. An interesting story of the human being in his conquest of the air as seen through the eyes of the flight surgeon is unfolded. In the early days of aviation little thought was given to the man at the controls on whom must rest the successful performance of the most perfectly designed and constructed planes. The stress and strain on the nervous and circulatory systems were little understood and the high accident rate was promptly reduced when attention was drawn to the physical requirements of flying. The author describes the pioneering studies made during the war to support the human body in an unusual environment, as nature never intended that man should fly. The mounting toll of accidents directed attention to physical defects in the pilots and a basic rule was at once established: that only the physically fit shall fly. After a searching general physical examination, studies were directed to the eyes, muscle balance, the ear as a dual sense organ, effects of diminished oxygen, muscular coordination and nervous reaction times, resulting in an examination outline which is the basis of the one in use today by the army, the navy and the department of commerce. A special chapter is devoted to blind flying and clearly explains its development and universal use in modern aviration—a distinct contribution from the flight surgeon. All who have flown, are flying and expect to fly should read this interesting book. It portrays preventive medicine in its highest form and reveals why "the planes go through."

Medizinische Praxis: Sammlung für ärztliche Fortbildung. Herausgegeben von Prof. Dr. L. R. Grote, leitender Arzt der medizinischen Klinik des Rudolf-Hess-Krankenhauses Dresden, Prof. Dr. A. Fromme, Direktor der chirurgischen Abteilung des Stadtkrankenhauses Dresden-Friedrichstadt, und Prof. Dr. K. Warnekros, Direktor der staatlichen Frauenklinik zu Dresden. Band XXIV: Der Vitaminhaushalt in der Schwangerschaft mit besonderer Berücksichtigung der Vitamine A und C. Von Dr. med. Gerhard Gaehtgens, Universitätsfrauenklinik zu Leipzig. Paper. Price, 12 marks. Pp. 161, with 21 illustrations. Dresden & Leipzig: Theodor Steinkopff, 1937.

In this small book the author reviews the literature and his own studies on the vitamin requirements during pregnancy. He first discusses the metabolism of proteins, carbohydrates, fats, lipoids, ions and chlorides during pregnancy. He then considers the relationship of vitamins and hormones to the body metabolism. The greater portion of the book, however, is devoted to information concerning the importance of vitamins A and C in pregnancy. The author gives in great detail the chemistry, source, methods of detection, effects and results of lack of both of these vitamins for the nonpregnant. A special chapter is assigned to a discussion of vitamins A and C in pregnancy, and separate chapters are given over to the importance of these two hormones for the fetus and for lactation.

The author also discusses the antagonism between the thyroid gland and vitamins A and C and the effect of this on pregnancy and lactation. At the end of the book is a useful chart of foods and the amount of vitamins A, B_1, B_2, C, D and E which they contain. There is also an extensive bibliography. The book is well written and will serve admirably as a source of information for vitamins in general and for the vitamin requirements of pregnancy in particular. The price of the book is, however, ludicrously high for an unbound monograph containing twenty-one small charts.

Practical Physiological Chemistry. By Philip B. Hawk, M.S., Ph.D., President of the Food Research Laboratories, Inc., New York City, and Olaf Bergeim, M.S., Ph.D., Associate Professor of Physiological Chemistry, University of Illinois College of Medicine, Chicago. In collaboration with Bernard L. Oser, Ph.D., Director of the Food Research Laboratories, Inc., New York City, and Arthur G. Cole, Ph.D., Assistant Professor of Physiological Chemistry, University of Illinois College of Medicine, Chicago. Eleventh edition. Cloth. Price, $8. Pp. 968, with 281 illustrations. Philadelphia: P. Blakiston's Son & Company, Inc., 1937.

This is the oldest American textbook in physiologic chemistry. Hawk was a student of Chittenden, who started the first laboratory of physiologic chemistry in the United States and, doubtless, many of the experiments have been elaborated by Chittenden or his students. Although more detailed laboratory work of Folin and Van Slyke has been collected in two other books, Hawk and Bergeim have supplied the most complete collection of selected laboratory methods, which include not only the chemistry of proteins, fats and carbohydrates but physical chemistry in relation to physiology. The main part of the book treats of the chemistry of tissues and foods, enzyme action and digestion, absorption, putrefaction and excretion, and respiratory metabolism (including calculations of total energy exchange) and hormones and vitamins. In the two latter groups chemical methods are used when possible, but biologic methods are described when chemical methods fail or are nonspecific. The book is in general well balanced, with few errors. Some points are not absolutely clear; for instance, it would appear to be implied on page 66 that methylphenylfructosazone is different from the corresponding glucosazone. The melting point is too low. On page 81 it seems implied that the main bulk of ingested agar passes into the feces, whereas a number of investigators have found that it is mainly decomposed by bacteria. On page 243, papaya is called paw-paw, which is an entirely different fruit. The formula for adenylpyrophosphate on page 779 does not seem possible. A method for the prevention of glycolysis in blood was not found but otherwise methods of analysis as well as preservation of specimens are rather completely covered.

The American Medical Profession 1783 to 1850. By Henry Burnell Shafer, Ph.D. Number 417, Studies in History, Economics and Public Law. Edited by the Faculty of Political Science of Columbia University. Cloth. Price, $3.25. Pp. 271. New York: Columbia University Press; London: P. S. King & Son, Ltd., 1936.

Here a competent medical historian surveys a period in the history of American medicine not adequately surveyed previously. The period concerned comprises that in which the American Medical Association was founded; the author's account of that event is most interesting. The concluding chapter deals with the developments in scientific medicine in the period concerned. In 1850 there were twenty-four medical journals in the United States, and just a few textbooks were being printed in this country. The volume concludes with the prediction of Samuel Gross, made in 1861, that a great new era was about to commence.

A Text-Book of Mental Deficiency (Amentia). By A. F. Tredgold, M.D., F.R.C.P., F.R.S.E., Lecturer on Mental Deficiency, London University. Sixth edition. Cloth. Price, $7.50. Pp. 556, with 34 illustrations. Baltimore: William Wood & Company, 1937.

The fifth edition of this book appeared in 1929. In the intervening eight years there have been great advances, which the author has endeavored to reflect in his book. The volume is one of the best available on this subject and is useful both as a textbook and as a work of reference. One of the most fascinating chapters and one not usually seen in similar books on the subject is that headed "Idiots Savants."

An Analysis of the De Generatione Animalium of William Harvey. By Arthur William Meyer, Professor of Anatomy, Stanford University. Boards. Price, $3. Pp. 167, with 11 illustrations. Stanford University, California: Stanford University Press; London: Oxford University Press, 1936.

While William Harvey is chiefly noted for his book entitled "De motu cordis," which concerns the circulation, the volume here discussed, and largely quoted as well, has aroused great interest and study among physicians throughout the world. It is essentially an early work in embryology and as such deserves medical consideration. Harvey was a philosopher as well as a scientist. It is interesting to know that more than 300 years ago he warned against meddlesome midwifery.

Treatment in Psychiatry. By Oskar Diethelm, M.D., Professor of Psychiatry, Cornell University Medical College, New York. Cloth. Price, $4. Pp. 476. New York: Macmillan Company, 1936.

This volume is based on the principle that the patient rather than the symptoms requires treatment. It is a study of personality, including an excellent historical survey of various methods of procedure in psychiatry now available. The cases presented for analysis and study are found to be well selected and exceedingly interesting. The division of psychiatry into excitement and depression, schizophrenic reactions, and paranoid, delirious and toxic reactions is an indication of the new broad lines which govern psychiatry today. This volume is sufficiently direct in its concept and in its presentation to warrant its use by every physician who wishes to orient himself in this field.

Physiology for Pharmaceutical Students. By Harold Hayden Barber, B.Sc., Ph.D., F.I.C., Head of the Sub-Department of Physiology in the University College of Nottingham, Nottingham. Cloth. Price, $2. Pp. 477, with 132 illustrations. Baltimore: William Wood & Company, 1937.

This book attempts to give students of pharmacy an insight not only into physiology but also into pharmacology, which is indeed a happy combination to aim at in such a course. The book is especially noteworthy for its detailed description of laboratory exercises at the end of nearly every chapter. It must be regretfully admitted that there are few if any pharmacy schools in this country that give their pupils any such comprehensive course in physiology. Indeed, even the text in its general comprehensiveness would probably be "beyond" the comprehension of the average student in our pharmacy schools at present.

Twins: A Study of Heredity and Environment. By Horatio H. Newman, Frank N. Freeman and Karl J. Holzinger. Cloth. Price, $4. Pp. 369, with 72 illustrations. Chicago: University of Chicago Press, 1937.

In this volume, which is probably the most complete and most important study ever made of the biology, mentality and incidence of twins, a leading biologist, an educator and a statistician have combined. The book includes three parts devoted to the biology of twins, a comparison of fifty pairs of identical twins and fifty pairs of fraternal twins and, finally, a study of nineteen pairs of identical twins separated in infancy. The work concludes with a summary that indicates the extent to which character is determined by constitution and by environment, the final conclusion of the authors being that what heredity can do environment can also do. Notwithstanding the inability of the authors to state any positive conclusions, the study is of immense interest and highly suggestive for all concerned with similar questions.

Ein Leben als Arzt der Seele. Erinnerungen. Von Albert Moll. Paper. Price, 3.37 marks. Pp. 282. Dresden: Carl Reissner Verlag, 1936.

The career of Albert Moll in psychiatry, in the field of hypnotism and in the study of sex is widely known through his great works on these subjects. Here he recapitulates the development of his scientific life. By this recapitulation he indicates how completely removed the scientist may be from the human being or the philosopher in any man.

The Silver Kings of Aransas Pass and Other Stories. By Richard L. Sutton, F.R.G.S. Cloth. Price, $1. Pp. 352, with one illustration. Kansas City, Missouri: Brown-White Company, 1937.

The amateur but ardent fisherman or sportsman will find these brief descriptions of the author's excursions with rod and gun of considerable charm. They form a collection of experiences during approximately twenty years, from 1917 to 1937, and may tempt the reader to cast in new waters.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Workmen's Compensation Acts: Insanity as a Compensable Injury.—In 1928 a car ran over the workman's right foot. The attending physician was unable to find any fracture or condition that would prevent the workman from returning to work. Nevertheless he quit work and developed what the record describes as a "bad mental condition," in which notions of injustice and persecution in connection with his claim for compensation which he filed predominated. A claim for compensation under the workmen's compensation act of Michigan was at that time denied. Subsequently, in 1934, he killed a man whom he thought was trying to steal papers relating to his claim and he was confined in a state hospital as a criminally insane person. His right leg had become weakened from disuse, partly at least arising out of his idea that he could not use it. His claim for compensation was again considered and an award was made by the department of labor and industry. The employer then appealed to the Supreme Court of Michigan.

That the workman had become worse, both physically and mentally, said the court, since the hearing was undisputed. The present case posed the question as to whether and when disability arising from a mental disorder growing out of an accident is compensable. The authorities plainly indicate, the court said, that where the accident has a direct effect on the nervous system, all the results thereof, both physical and mental, go to make up disability and determine compensability. Where, however, the mental disturbance is collateral to the injury and is due to worry, anxiety or brooding over the accident or its effect on compensation for it, it is not compensable. In the present case, the court said, the distinction was not kept in mind in the presentation of testimony or in the opinion of the commission. It found the fact of total disability without a proper regard for the applicable rule of law. The issue was whether and how far the workman's disability was the direct result of the physical injury to his foot, excluding the consequences of mental disturbances collateral to and not arising directly from the physical hurt. Since this issue was not adjudicated by the commission, the Supreme Court vacated the award and remanded the case for the reconsideration of the commission.—*Schneyder v. Cadillac Motor Car Co. (Mich.), 273 N. W. 418.*

Medical Practice Acts: Use of Title "Doctor" by Drugless Healer as Cause for Revocation of License.—In 1924 the defendant, Wicker, was granted a license by the Michigan state board of medical registration in medicine to practice a system of treatment of human ailments or diseases without the use of drugs. The provisions of the medical practice act under which Wicker was licensed denied him the right to use the title "Doctor." In 1936 a notice was served on Wicker requesting him to appear before the board and show cause why his license should not be revoked or suspended (1) because of his having used the title "Doctor," (2) because of his having exceeded and violated the terms and conditions under which he was licensed, and (3) because of his having represented himself to be qualified to practice medicine. Following the hearings the board revoked the license and Wicker appealed to the Supreme Court of Michigan.

The testimony showed that Wicker was an ordained minister of the Christian Spiritualist Association. His healing methods were both religious and drugless, the latter performed by manipulation of the muscles and nerves of the patient's body. After the testimony had been concluded, the board found Wicker guilty of "(1) using the title 'Dr.,' representing himself as a physician; (2) advertising of grossly improbable statements; (3) failing to limit his practice to the scope of authority conferred." But, said the Supreme Court, the notice served on Wicker did not contain a charge that he was guilty of the "advertising of grossly improbable statements." A physician cited to appear and answer specific charges should not be charged with one type of misconduct and on hearing be convicted of another and wholly different type of misconduct not contained within the charges made and served on him. For this reason the revocation of Wicker's license on this ground could not be sustained. Furthermore, the notice served on Wicker charged him with having exceeded and violated the terms and conditions under which he was licensed to practice by administering treatments not within the scope of his license. With respect to this charge, said the Supreme Court, it must first be noted that it was not sustained by any testimony and, secondly, that it was too indefinite to be used as the basis of a lawful hearing of this character.

A careful review of the record convinced the court that the only charge established against the defendant which was sufficiently stated in the notice served on him was that he unlawfully used the title "Doctor." As a matter of fact, such use was admitted but Wicker contended that this use did not constitute a ground on which the board could base its revocation order. While the provisions of the act under which Wicker was licensed specifically denied him the right to use the title "Doctor," the provisions of the medical practice act specifying the causes for which a license could be revoked neither expressly nor by fair implication included the improper use of the title "Doctor." It follows, the court said, that the board, a purely statutory body having only statutory powers, was without authority to suspend or revoke the defendant's license because of his improper use of the title "Doctor." The order of the board of registration in medicine revoking the defendant's license was therefore set aside.—*State Board of Registration in Medicine v. Wicker (Mich.), 274 N. W. 343.*

Society Proceedings

COMING MEETINGS

Alabama, Medical Association of the State of, Mobile, Apr. 19-21. Dr. D. L. Cannon, 519 Dexter Ave., Montgomery, Secretary.

American Association for Thoracic Surgery, Atlanta, Ga., Apr. 4-6. Dr. Richard H. Meade Jr., 2116 Pine St., Philadelphia, Secretary.

American Association of Anatomists, Pittsburgh, Apr. 14-16. Dr. George W. Corner, 260 Crittenden Blvd., Rochester, N. Y., Secretary.

American Association on Mental Deficiency, Richmond, Va., Apr. 20-23. Dr. E. Arthur Whitney, Washington Road, Elwyn, Pa., Secretary.

American Bronchoscopic Society, Atlantic City, N. J., Apr. 30. Dr. Lyman Richards, 319 Longwood Ave., Boston, Secretary.

American College of Physicians, New York, Apr. 4-8. Mr. E. R. Loveland, 4200 Pine St., Philadelphia, Executive Secretary.

American Laryngological, Rhinological and Otological Society, Atlantic City, N. J., Apr. 27-29. Dr. C. Stewart Nash, 277 Alexander St., Rochester, N. Y., Secretary.

American Physiological Society, Baltimore, Mar. 30-Apr. 2. Dr. A. C. Ivy, 303 East Chicago Ave., Chicago, Secretary.

American Society for Experimental Pathology, Baltimore, Mar. 30-Apr. 2. Dr. Paul R. Cannon, University of Chicago, Chicago, Secretary.

American Society for Pharmacology and Experimental Therapeutics, Baltimore, Mar. 30-Apr. 2. Dr. G. Philip Grabfield, 319 Longwood Ave., Boston, Secretary.

American Society of Biological Chemists, Baltimore, Mar. 30-Apr. 2. Dr. H. A. Mattill, Chemistry Bldg., State University of Iowa, Iowa City, Secretary.

American Therapeutic Society, New York, Apr. 1-2. Dr. Oscar B. Hunter, 1835 Eye St. N.W., Washington, D. C., Secretary.

Arizona State Medical Association, Tucson, Apr. 21-23. Dr. D. F. Harbridge, 15 East Monroe St., Phoenix, Secretary.

Arkansas Medical Society, Texarkana, Apr. 18-20. Dr. W. R. Brooksher, 602 Garrison Ave., Ft. Smith, Secretary.

Federation of American Societies for Experimental Biology, Baltimore, March 30-April 2. Dr. D. R. Hooker, 19 West Chase St., Baltimore, Secretary.

Georgia, Medical Association of, Augusta, Apr. 26-29. Dr. Edgar D. Shanks, 478 Peachtree St. N.E., Atlanta, Secretary.

Maryland, Medical and Chirurgical Faculty of, Baltimore, Apr. 26-27. Dr. Walter Dent Wise, 1211 Cathedral St., Baltimore, Secretary.

Mississippi State Medical Association, Jackson, Apr. 19-21. Dr. T. M. Dye, McWilliams Bldg., Clarksdale, Secretary.

Nebraska State Medical Association, Lincoln, Apr. 26-28. Dr. R. B. Adams, Center-McKinley Bldg., Lincoln, Secretary.

Philippine Islands Medical Association, Zamboanga City, Apr. 19-22. Dr. A. S. Fernando, 817 Taft Ave., Manila, Secretary.

Southeastern Surgical Congress, Louisville, Ky., March 7-9. Dr. B. T. Beasley, 701 Hurt Bldg., Atlanta, Ga., Secretary.

Tennessee State Medical Association, Nashville, Apr. 12-14. Dr. H. H. Shoulders, 706 Church St., Nashville, Secretary.

CENTRAL SOCIETY FOR CLINICAL RESEARCH

Tenth Annual Meeting, Held in Chicago, Nov. 5 and 6, 1937

The President, DR. DAVID P. BARR, St. Louis, in the Chair

(Continued from page 688)

Severe Anemia in Puppies on a Synthetic Diet Deficient in Rat Antidermatitis Factor (Vitamin B_6)

DRS. PAUL J. FOUTS, Indianapolis; O. M. HELMER, Indianapolis; SAMUEL LEPKOVSKY, Berkeley, Calif., and THOMAS H. JUKES, Berkeley, Calif.: Puppies grew satisfactorily on a diet composed of casein, sucrose, crisco, bone ash and salt mixture 185 when supplemented with halibut liver oil; vitamin B_1, either crystalline or a vitamin B_1 concentrate prepared by the method of Stuart, Block and Cowgill; riboflavin; liver filtrate containing chick antidermatitis factor or filtrate factor, and a rice polish extract containing the rat antidermatitis factor (vitamin B_6). However, the puppies on this diet similarly supplemented except for the absence of the rice polish extract (vitamin B_6), which had been shown to be free from both riboflavin and the filtrate factor, not only did not show proper growth but developed a severe microcytic hypochromic anemia often associated with neurologic symptoms. This anemia did not respond to an increase of iron in the diet. The addition of the rice polish extract to the diet produced a reticulocytosis followed by a rapid increase in weight, red blood cell count and hemoglobin percentage. The puppies on this diet and all the supplements but the liver filtrate factor developed signs and symptoms of blacktongue.

DISCUSSION

DR. CHARLES A. DOAN, Columbus, Ohio: Were white counts and platelet counts done in the dogs with vitamin B_6 deficiency?

DR. PAUL J. FOUTS, Indianapolis: The white counts were not remarkable. There might have been a slight decrease from the original count of 15,000 or 20,000 to 13,000, 12,000 or 11,000. The platelets were not counted but there did not appear to be a decrease on the smear.

Yellow Bone Marrow in the Treatment of Agranulocytic Angina and Secondary Granulocytopenia

DRS. C. H. WATKINS and H. Z. GIFFIN, Rochester, Minn.: During experimental studies with the administration of bone marrow for secondary anemia in 1928 and 1929, a moderate increase in the number of monocytes and neutrophils was observed in blood smears. This observation led to the administration of bone marrow in cases of granulocytopenia. The first case of agranulocytic angina was treated with bone marrow in July 1930. Since then more than twenty cases have been treated with bone marrow, with no other treatment aside from nursing care. During the acute stage from 200 to 400 grains (13 to 26 Gm.) of bone marrow was given daily; one patient took as much as 800 grains (52 Gm.) daily. As monocytes and polymorphonuclears appeared in the blood smears the dose was decreased. Death occurred in only three of those cases in which an adequate amount of bone marrow could be ingested, and in these cases there were severe complications. In every case in which an adequate amount of bone marrow could be administered and in which complications were not overwhelming, there was a favorable reaction in the blood and general condition of the patient with recovery from the attack.

DISCUSSION

DR. S. MILTON GOLDHAMER, Ann Arbor, Mich.: Since Madison and Squier demonstrated that aminopyrine was a causative agent in agranulocytic angina, other investigators have shown a similar relationship to agranulocytosis with such drugs as gold compounds, dinitrophenol and sulfanilamide. Before any specific etiologic factor was determined, the majority of patients with this disease died. However, with the elimination of the drug which produced agranulocytosis, there have been very few deaths, regardless of the type of supportive therapy used. It appears from these facts that the important feature of treatment is the removal of the cause. I wonder whether the results of Drs. Watkins and Giffin may not be attributed to the removal of the etiologic factor as well as to the oral administration of yellow bone marrow.

DR. CHARLES A. DOAN, Columbus, Ohio. Were any extensive bone marrow studies made in addition to the blood studies before and after treatment?

DR. TOM D. SPIES, Cleveland: How was an adequate dose determined? How was the bone marrow given?

DR. C. H. WATKINS, Rochester, Minn: Most of these cases of agranulocytosis were treated before it was suspected that aminopyrine and other similar substances were important etiologic factors. In some instances the use of aminopyrine was continued throughout the time the patient was under treatment. In certain other cases we have been able to eliminate the possibility of any of these drugs being used and yet have noticed a rapid remission in the disease with bone marrow. We have more or less arbitrarily, as a result of experience, selected 300 grains (20 Gm.) of bone marrow extract daily as the average dose. In mild leukopenic states smaller doses of from 75 to 100 grains (5 to 6.5 Gm.) have been given. In severe leukopenic states as much as 800 grains (52 Gm.) daily has been given. If there is no improvement in the leukocyte count and no evidence of monocytes in the peripheral blood following the initial dose of 300 grains (20 Gm.) the dose is increased usually to 400 or 500 grains (26 to 32.5 Gm.) daily until some change is noted in the peripheral blood. We have not studied the changes in the bone marrow in this group. This would be of great interest during the recovery phase of the disease and it would also be of interest to note whether the state of the bone marrow at the time the administration of bone marrow extract is started has anything to do with the type of response obtained.

Administration of Nicotinic Acid to Pellagrins

DRS. TOM D. SPIES, CLARK COOPER and M. A. BLANKENHORN, Cincinnati: Since pellagra in human beings and blacktongue in dogs are often regarded as closely related diseases, and since Elvehjem and his associates had reported the cure of canine blacktongue by the use of nicotinic acid, it seemed worth while to determine whether this substance would be beneficial in the treatment of human pellagra. Preliminary observations showed that nicotinic acid could be given safely either orally or parenterally. Four pellagrins were selected for study. Two were male chronic alcoholic addicts with characteristic pellagrous dermatitis, glossitis and stomatitis. The third was a female chronic alcoholic addict with pellagrous dermatitis, glossitis, stomatitis and vaginitis. The fourth, a woman, did not use alcohol but acquired pellagrous dermatitis, glossitis, stomatitis and vaginitis following subsistence on a deficient diet over a period of five years. On admission to the hospital each patient was placed under controlled conditions. During the test period the three patients whose pellagra followed chronic alcoholic addiction received only small amounts of a basic (pellagra-producing) diet and nicotinic acid. Two of these patients, who had involvement of the nervous system, received crystalline vitamin B_1 in addition to the basic diet and nicotinic acid. The fourth patient, whose disease was unassociated with alcoholic addiction, was so ill that she was unable to eat any food. She received only parenteral injections of nicotinic acid, crystalline vitamin B_1, saline solution and dextrose until the stomatitis and glossitis had definitely improved. Within twelve hours after the administration of nicotinic acid the oral lesions of all four pellagrins, as well as the vaginal lesions of the two women, were distinctly less red. One man whose disease followed chronic alcoholic addiction continued to eat the basic diet for three weeks and received 50 mg. of nicotinic acid three times each day by mouth. There was no return of the dermal or oral lesions of pellagra. This study shows that the fiery red color associated with the pellagrous dermatitis, glossitis, stomatitis and vaginitis of these four patients improved under the conditions of this study. Although it must be admitted that observations on pellagrins during the past seven years have shown that the lesions of an occasional pellagrin disappear while he is taking a basic pellagra-producing diet, the pellagrins in whom such "spontaneous" remissions have been observed have not been as severely ill nor did their symptoms improve as promptly as did the ones in the present study.

DISCUSSION

DR. PAUL J. FOUTS, Indianapolis: About a year ago Drs. Lepkovsky, Helmer, Jukes and I reported the successful treatment of pellagra with a filtrate factor which is similar to that from which the group at Wisconsin isolated nicotinic acid. We had four patients recently treated with nicotinic acid with as satisfactory results as Dr. Spies and his co-workers obtained.

DR. JOHN W. MOORE, Louisville, Ky.: I should like to ask about the skin lesions.

DR. M. A. BLANKENHORN, Cincinnati: In one of the most acute cases there were severe lesions of the tongue and the vagina. The patient was unable to eat. We gave her only water and nicotinic acid. The vaginal lesions which were so fiery red cleared up as well as the lesions of the tongue.

DR. MOSES BARRON, Minneapolis: What is the dose of nicotinic acid in the treatment of these cases?

DR. TOM D. SPIES, Cincinnati: Since Dr. Fouts and his co-workers have been so unusually successful in their work in the field of deficiency diseases, it is particularly gratifying that their results are in agreement with our own. In answer to Dr. Moore's question, the four pellagrins we described did have typical pellagrous dermatitis. However, I would hesitate to say what effect the nicotinic acid might have had on the skin lesions. We have shown previously that the skin lesions are never static and that the tendency to improve is strong even though the patient may eat a pellagra-producing diet. It will take further studies in order to settle this pertinent point. We purposely avoided mentioning dosage, as it is still in the experimental stage. We have given a pellagrin as much as 0.5 Gm. daily without ill effects. Healing of the glossitis and stomatitis of several of the pellagrins occurred on much smaller amounts of nicotinic acid. We have no information, however, as to what the minimal effective dose for these patients might have been.

The Iodine Balance in Exophthalmic Goiter

DRS. ITALO D. PUPPEL and GEORGE M. CURTIS, Columbus, Ohio: Three normal persons on a low iodine intake averaging 87 micrograms to each three day period remained in continuous negative iodine balance. Three patients with exophthalmic goiter maintained on a similar low iodine intake revealed an increased mobilization of iodine, an increase in its circulation, and an increase in its excretion through one or all excretory channels. This resulted in a profound disturbance of the iodine balance. Increased iodine feeding to a normal person produced an immediate positive iodine balance. Similar increased iodine feeding to a hyperthyroid patient resulted in an immediate tremendous retention of iodine with a positive iodine balance, which was twice the normal. The increased negative iodine balance of hyperthyroidism returned to within normal limits subsequent to adequate thyroid surgery.

DISCUSSION

DR. ROBERT W. KEETON, Chicago: Are there criteria to determine iodine saturation other than decrease in metabolic rate?

DR. M. A. BLANKENHORN, Cincinnati: Is there any difference in the terms of iodine output in that phase of the disease which is said to be an "escape" from iodine control? When iodine is given a patient with thyrotoxicosis and the patient improves, sooner or later the improvement ceases. Have you information concerning the effect of iodine in that phase of the disease?

DR. ITALO D. PUPPEL, Columbus, Ohio: Our iodine balance researches have not extended as yet into problems concerned with iodine saturation and escape from iodine control during the iodine treatment of exophthalmic goiter. Iodine metabolism investigation of the latter phases of iodine therapy should prove of the greatest interest.

The Treatment of Hypoparathyroid Tetany with Dihydrotachysterol

DR. CYRIL M. MACBRYDE, St. Louis: Studies were presented of four patients with parathyroprivic tetany relieved by dihydrotachysterol. The results with the various combinations of the usually accepted methods of treatment, including large doses of calcium by mouth, acid salts, viosterol, low phosphorus diets and parathyroid extract, were compared with the response to the new drug. In these patients, all previously under treatment for some years, the usual medications have been unsuccessful in preventing the development of cataracts. One patient developed severe epileptiform convulsions. The new medication has for the first time made it possible to achieve and maintain normal blood calcium levels and to relieve symptoms completely. Two of these patients have had approximately normal blood calcium and no symptoms for nine months and the other two for three months each. It seems advisable, although not absolutely necessary, to give small doses of calcium with the dihydrotachysterol. It must be emphasized that this very potent preparation should not be used indiscriminately. Excessive doses have been shown to result in decalcification of bone of experimental animals and greatly increased urinary calcium, metastatic calcification, severe gastro-intestinal upsets, and bleeding from the bowel. Studies with this drug should be undertaken only with the greatest of care. Frequent determination of serum calcium is necessary. It seems probable that this fraction of irradiated ergosterol will prove of considerable importance in the treatment of hypoparathyroidism. Certainly no other preparation in our hands has given such excellent results in the treatment of tetany. Calcium and phosphorus balance studies were done on two patients to investigate the mode of action of the dihydrotachysterol on calcium and phosphorus metabolism. In these preliminary studies we were unable to demonstrate an increased absorption of calcium with the drug. Further studies are being pursued along this line.

DISCUSSION

DR. W. S. MIDDLETON, Madison, Wis.: I will add two cases using A. T.-10 (dihydrotachysterol) that we have had at Madison, one with latent tetany of three years' duration and the other an acute tetany of a month's duration. In both with maintenance doses of 1 cc. the patients remained free from symptoms and maintained satisfactory blood calcium levels.

DR. W. E. POST, Chicago: Over how long a period is the administration of dihydrotachysterol continued?

DR. WILLIAM S. HOFFMAN, Chicago: The rise in serum calcium after dihydrotachysterol seems all the more dramatic in that it took place with a high intake of phosphorus. I should like to ask in this connection whether the authors have tried to use a very low phosphorus diet without dihydrotachysterol, in view of Shelling's reported success in managing tetany this way.

DR. E. P. MCCULLACH, Cleveland: The action of this material is remarkable in many ways, not only in its power to raise the blood calcium but in the great similarity of its action to parathyroid extract itself. The studies on the blood calcium show that it not only raises the serum calcium levels but has a tendency to lower the blood phosphorus considerably. Caution is needed in using this substance. A daily dose tends to accumulate in its activity over a few days, so that the rise in serum calcium that takes place tends to continue, particularly if the first few doses are large. I wonder whether the amount of calcium that is apparently thrown out of the system under the action of this material, being similar to the action of parathyroid extract may not be another reason for extreme caution in the use of this potent drug.

DR. CYRIL M. MACBRYDE, St. Louis: The drug must be continued in small maintenance doses to keep the blood calcium at normal levels. Our patients are taking from 0.25 to 0.75 cc. daily, with a calcium intake ranging from 2 to 10 Gm. of calcium lactate or gluconate. The phosphorus intake averaged about 1 Gm. daily in these patients. During these studies no attempt was made to restrict greatly the phosphorus ingested. Previously, however, several of the patients have had low phosphorus diets, which would seem to be somewhat helpful in their treatment. When A. T.-10 (dihydrotachysterol) is used there seems to be no necessity for severe restriction of the phosphorus intake. After the drug was started there was a gradual increase in both blood phosphorus and blood calcium. Then as the calcium continued to rise there was a tendency for the blood phosphorus to fall. The apparently cumulative effect of the drug is important. The drug exerts its action over a period of days or weeks and it takes several days for any marked effect to appear. In a

week or two the blood calcium reaches normal levels on doses of from 0.5 to 2 cc. a day. Holtz gave 10 cc. the first day, 5 the second day and 2 every day thereafter. Such large doses do not seem to be necessary and we have not used them because of the danger of producing hypercalcemia.

Experimental Insulin-Sensitive and Insulin-Insensitive Diabetes

DRS. SAMUEL SOSKIN and R. LEVINE, Chicago: The differentiation between the insulin-sensitive (juvenile or unstable) type of diabetes and the insulin-insensitive (adult or stable) type is of considerable clinical interest. The insulin-insensitive type has been found to give a better response than the other to high carbohydrate diets. From the theoretical standpoint the resemblance of the insulin-sensitive type to the depancreatized animal has led to the suggestion that this type of diabetes is probably due to a lack of endogenous insulin, while the insulin-insensitive type has been ascribed to extrapancreatic disturbances. We have been able to reproduce both types of diabetes in the same completely depancreatized dog, at different times. There was no endogenous supply of insulin at either time. The significant difference between the two types of diabetes has been found to depend on the functional capacity of the liver.

DISCUSSION

DR. W. S. HOFFMAN, Chicago: Can the response of the blood dextrose concentration to the injection of insulin be used as an index of liver function?

DR. MOSES BARRON, Minneapolis: The result seemed excellent with pancreatic feedings in depancreatized dogs. May there not be specific changes in the liver as a result of the pancreatic feedings, and may not that change the sugar tolerance? Feedings other than pancreas should be tried.

DR. E. P. MCCULLACH, Cleveland: It has been well known for a long time that depancreatized animals finally do go into hypocalcemia if not fed pancreas, and the same phenomenon can be prevented if they are fed lecithin and similar substances. I wonder whether Dr. Soskin believes that the stable type of diabetes in man is the result of fatty metamorphosis such as takes place in animals.

DR. CYRIL MACBRYDE, St. Louis: I am gratified that Dr. Soskin has been able to confirm our observations distinguishing the two main types of diabetes—the relatively insulin resistant and the relatively insulin sensitive. Continued observations on the previously reported group of patients and a number of other patients since added to our studies have confirmed our belief that the insulin-sensitive type of patient shows little or no gain in carbohydrate tolerance no matter what type of diet he takes. On the other hand, the insulin-resistant type shows a definite tendency to gain tolerance, especially if allowed a high carbohydrate intake. I believe that Dr. Soskin's studies revealing the importance of the liver may show the usual cause of the relative insulin resistance seen in at least half of our diabetic patients. There are, of course, other features which may be important in reducing the effectiveness of endogenous or exogenous insulin. The dramatic effects sometimes following the removal of adrenal tumors or the treatment of pituitary lesions afford examples of factors which are probably more infrequent.

DR. SAMUEL SOSKIN, Chicago: In reply to Dr. Hoffman's question the hypoglycemic effect of insulin probably could be used as a test of liver function with about as much justification as many other liver function tests. However, like these other function tests it would give information about only one of the many functions of the liver and, in addition, it would be subject to many extrahepatic influences that are difficult to control. As regards Dr. Barron's question concerning the production of fatty changes in the liver by means other than omitting the raw pancreas from the diet of our depancreatized dogs, we expect to have such data before this work is completed. There is, of course, the possibility that fatty changes and liver dysfunction produced by other means might not be accompanied by similar changes in the character of the diabetes. However, in my opinion, this possibility is remote. Dr. McCullagh's question concerning the possibility that the stable type of human diabetic patient has a fatty liver is a good one. In this connection the efficacy of the high fat diet in controlling diabetic manifestations has puzzled me for a long time. While this was quite in line with the older ideas on diabetic metabolism, it is difficult to explain on the basis of our newer knowledge. It may be that the moderate fatty infiltration of the liver caused by high fat diets accounts for the beneficial effects of this treatment. Anything that mildly limits the functional capacity of the liver will similarly cause apparent improvement of the diabetes. However, these remarks are speculative and remain to be proved. Regarding Dr. MacBryde's work showing that the insulin-sensitive diabetic patient shows no gain in tolerance on any diet, that is quite consistent with our results. The sensitive or juvenile type of diabetic patient, with a normal liver, responds maximally to insulin. Thus one would not expect to be able to improve his tolerance, as judged by his insulin-dextrose equivalence, by any form of diet. In the adult type of patient with diabetes there is a reduced liver function. Hence a high carbohydrate diet, by improving liver function, will increase its responsiveness to insulin, and the insulin-dextrose equivalent is increased.

Influence of Insulin on Protein Metabolism

DR. I. ARTHUR MIRSKY, Cincinnati: Although much is known concerning the role of insulin in carbohydrate and fat metabolism, its function in protein metabolism is still problematic. In a series of experiments performed with fasted normal and eviscerated dogs, we have obtained data which indicates that insulin always decreases the rate of protein metabolism. This is accomplished by two mechanisms: (1) inhibition of hepatic deaminization and (2) increased utilization of amino acids by the muscles. Data were also obtained which revealed that increasing the amino acid content of the blood to high levels results in a diminution in amino acid elimination by the muscle. These studies suggest that insulin may be of therapeutic value in muscular wasting diseases of various kinds.

DISCUSSION

DR. SAMUEL SOSKIN, Chicago: This study points to a further departure from the old view regarding insulin. Physicians have been gradually getting away from the idea that insulin is a hormone which promotes a specific effect (oxidation) in a single organ (muscle) and have come to regard it as more general both in its effects and in its locus of action. This work shows that we must now enlarge our point of view still more, to include protein as well as carbohydrate metabolism. I should be interested to know what success Dr. Mirsky has had with the insulin treatment of muscular dystrophies.

DR. E. H. RYNEARSON, Rochester, Minn.: Until protamine insulin became available, most men interested in the treatment of diabetes made every effort to keep the urine of diabetic patients free from sugar. Since the advent of protamine insulin some men have been regarding glycosuria as a postprandial glycosuria and feel that this is not a manifestation of destruction of the patient's endogenous stores. I should like to ask Dr. Mirsky whether his studies have indicated any greater nitrogen-sparing action with protamine insulin than with regular insulin.

DR. I. ARTHUR MIRSKY, Cincinnati: In anticipation of Dr. Soskin's question, I have prepared a slide which indicates some of the possible uses of insulin in this respect. However, I must stress that our studies are still in the early experimental stages. We find it difficult to obtain an adequate number of cases. Monat in 1935 administered 10 units of insulin daily to a patient with progressive muscular dystrophy, and with a gain in the weight of his patient he reported encouraging results. Within the past forty-eight hours it has come to my knowledge that Meldolesi has been using insulin together with pancreatin in cases of progressive muscular dystrophy. He also reports encouraging results. At the onset of our studies we could not obtain any cases of progressive muscular dystrophy but did study several cases of myasthenia gravis. We now have three cases of myasthenia gravis under observation. The slide reveals that during the insulin period of treatment the general muscular power of a patient suffering from myasthenia gravis improved about 600 per cent. With the cessation of insulin therapy the muscle power returned to its previous low state. This work is still in the early stages of experimentation. Our studies to date indicate that insulin may be of value in myasthenia gravis as well as in other muscular dystrophies.

(To be continued)

Current Medical Literature

AMERICAN

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Titles marked with an asterisk (*) are abstracted below.

American Journal of Cancer, New York

31: 537-710 (Dec.) 1937

Papillomatosis in Forestomach of Rat and Its Bearing on Work of Fibiger. W. Cramer, London, England.—p. 537.
Kaposi's Sarcoma. D. S. D. Jessup, New York.—p. 556.
Congenital Xanthoma Tuberosum. H. Charache, Brooklyn.—p. 563.
Comparison of Cytoplasmic Changes Induced in the Walker Rat Carcinoma 256 by Different Types and Dosages of Radiation: I. Golgi Apparatus. L. C. Fogg and S. Warren, Boston.—p. 567.
Id.: II. Mitochondria. L. C. Fogg and S. Warren, Boston.—p. 578.
Life Expectancy and Incidence of Malignant Disease: IV. Carcinoma of Genito-Urinary Tract. C. E. Welch and I. T. Nathanson, Boston.—p. 586.
Id.: V. Malignant Lymphoma, Fibrosarcoma, Malignant Melanoma and Osteogenic Sarcoma. I. T. Nathanson and C. E. Welch, Boston.—p. 598.
*Attempt to Induce a Specific Immunity to Transplantable Neoplasms. L. Gross, Paris, France.—p. 609.
Urine Chemistry in Diagnosis of Embryonal Tumors. S. E. Owen, Q. G. Polanco and L. H. Prince, Hines, Ill.—p. 613.

Immunity to Transplantable Neoplasms.—Gross avers that neoplasms induced in mice, rabbits and chickens by intracutaneous inoculation of emulsions of the Ehrlich sarcoma, Brown-Pearce rabbit carcinoma and Rous sarcoma, respectively, sometimes regressed spontaneously and the animals thereafter displayed a specific generalized immunity to inoculation with those tumors, which, however, was not transferable by blood serum or organ emulsions to other animals. Regression following subcutaneous inoculation of similar doses was unusual.

American Journal of Diseases of Children, Chicago

55: 1-230 (Jan.) 1938

Studies of Fetal Respiratory Movements: I. Historical and Present Day Observations. B. E. Bonar, C. M. Blumenfeld and C. Fenning, Salt Lake City.—p. 1.
*Influence of Vitamin C on Diphtheria Toxin. Jean Pakter and B. Schick, New York.—p. 12.
Metabolic Study of Five Children with Nephrotic Syndrome: I. Report on Certain Constituents of Blood, Basal Metabolism and Energy Exchange. A. G. Mitchell, C. R. Rittershofer, Chi Che Wang, Mildred Kaucher, Mary Wing and Corinne Hogden, Cincinnati.—p. 27.
Measurement of Obesity by Creatinine Coefficient. N. B. Talbot, with the assistance of Frances Broughton, Boston.—p. 42.
Results of Schick Test in 5,195 Children Given Injections of Diphtheria Toxoid. B. Benjamin, G. Fleming, Montreal, and Mary A. Ross, Toronto.—p. 51.
*Influence of Tonsillectomy on Rheumatic Infection. Rachel Ash, Philadelphia.—p. 63.
Role of Advanced Maternal Age in Causing Mongolism: Study of 2,822 Cases. A. Bleyer, St. Louis.—p. 79.
Hypertrophy of the Heart in Infants. H. E. MacMahon, Boston.—p. 93.
Gonadotropic Principle in Treatment of Cryptorchidism: Review of Literature. J. A. Bigler, Highland Park, Ill.; L. M. Hardy, Chicago, and H. V. Scott, Fort Wayne, Ind.—p. 100.
Scleremа Neonatorum (Subcutaneous Fat Necrosis). J. F. McIntosh, T. R. Waugh and S. G. Ross, Montreal.—p. 112.
Objective Ratings of Constitution of the Growing Child Based on Examination of Physical Development and Mental Expansion. T. W. Todd, Cleveland.—p. 149.

Influence of Vitamin C on Diphtheria Toxin.—Pakter and Schick studied the influence of vitamin C on diphtheria toxin in a series of children who were known to react positively to Schick tests done at varying intervals after the administration of cevitamic acid. All modes of administration—oral, intravenous, intramuscular, subcutaneous and intracutaneous—were tried. With all, the vitamin C was found to be ineffective if judged by the persistence of undiminished positive reactions to the Schick test even after doses as high as 1,100 mg. were given intravenously. A slight neutralizing effect of vitamin C was observed when it was mixed with diphtheria toxin in vitro and then injected intracutaneously. This effect was more apparent the longer the mixture was allowed to stand. The neutralizing effects of vitamin C are probably due to nonspecific inactivation brought about by changes in the p_H or by alterations due to changes made by the acid in the oxidation-reduction system or to both factors. A capillary effect due to vitamin C may be possible.

Influence of Tonsillectomy on Rheumatic Infection.—In view of the conflicting opinions, Ash made a study of the influence of tonsillectomy on the 532 rheumatic children who had come under observation in the ward or the cardiac disease clinic from 1922 to 1936. In eleven cases no definite information could be obtained from the records as to the presence or absence of tonsils at the time of the original infection, in ninety-six the tonsils had already been removed at the time of the first rheumatic manifestation and in 425 they were still present. Tonsillectomy did not prevent recurrences of rheumatic manifestations. Neither the presence nor the absence of tonsils at the time of the initial infection nor the removal of tonsils subsequent to the onset had any demonstrable influence on the incidence of cardiac involvement or the death rate. A tonsillectomy performed early in the course of the disease was followed immediately by a high incidence of rheumatic exacerbations. Tonsillectomy for the rheumatic child seems to be indicated only when there is definite evidence of disease in the tonsils and not as a routine procedure. The operation should be performed only during an inactive phase of the infection.

American Journal of Medical Sciences, Philadelphia

195: 1-140 (Jan.) 1938

Placenta as Modified Arteriovenous Fistula, Considered in Relation to Circulatory Adjustments to Pregnancy. C. S. Burwell, Boston.—p. 1.
Serial Blood and Bone Marrow Findings of an Eight Month Premature and Its Roentgen Ray Treated Chronic, Myeloid Leukemic Mother. L. A. Erf and A. Fine, Cincinnati.—p. 8.
Macrocytic Anemia in Cancer of Stomach, Apparently Due to Lack of Intrinsic Factor. S. M. Goldhamer, Ann Arbor, Mich.—p. 17.
Character of Leukocytic Response to Tuberculin in Sensitized Calves. J. Stasney and W. H. Feldman, Rochester, Minn.—p. 20.
Etiologic Relation of Eosinophil to Gordon Phenomenon in Hodgkin's Disease. J. C. Turner, H. Jackson Jr. and F. Parker Jr., Boston.—p. 27.
Study of Tuberculous Splenomegaly and Splenogenic Controlling of Cell Emission from Bone Marrow. J. Engelbreth-Holm, Copenhagen, Denmark.—p. 32.
Peculiar Form of Medial Calcification in Aorta of Dog. W. C. Corwin and R. W. Cragg, Rochester, Minn.—p. 47.
Xanthoma Diabeticorum Associated with Diabetes Mellitus and Acromegaly: Case. J. A. Buchanan and J. C. Indelicato, Brooklyn.—p. 50.
Photometric Studies of Visual Adaptation in Relation to Mild Vitamin A Deficiency in Adults. M. B. Corlette, J. B. Youmans, Helen Frank and Mildred G. Corlette, Nashville, Tenn.—p. 54.
Posttraumatic Internal Hydrocephalus. A. R. Moritz and W. B. Wartman, Cleveland.—p. 65.
*Assimilation of Protein by Young Children with Nephrotic Syndrome. L. E. Farr, New York.—p. 70.
Clinical Observations on Effects of Choline Compounds in Neurologic Disorders, with Especial Reference to Ménière's Syndrome. M. J. Cooper, San Antonio, Texas.—p. 83.
Human Autonomic Pharmacology: VII. Effect on Normal Cardiovascular System of Acetyl-Beta-Methylcholine Chloride, Atropine, Prostigmine, Benzedrine, with Especial Reference to Electrocardiogram. W. Dameshek, J. Loman and A. Myerson, Boston.—p. 88.
*Cause of Death in Coronary Thrombosis, with Especial Reference to Pulmonary Embolism. E. C. Eppinger and J. A. Kennedy, Boston.—p. 104.

Assimilation of Protein by Children with Nephrosis.—Farr observed five children, all 4 years of age, with the nephrotic syndrome, for fifty-four days on diets differing in the protein content. When the optimal level of protein intake for retention observed in the patients is compared with the optimum for normal children, the surprising fact becomes apparent that there are no marked differences between the two groups. Studies of other authors on the protein requirements of normal children have yielded results showing optimal growth and general condition with about the same protein intakes which yielded maximal nitrogen retention in the author's nephrotic children. Some of the results suggest that addition of fat beyond a certain amount decreases nitrogen retention. His

results offer no support for the thesis that in patients with albuminuria the optimal protein intake can be calculated by adding to the ordinary maintenance diet an amount of protein equal to or proportional to the loss of protein in the urine. The total failure to assimilate protein fed above 3.3 Gm. per kilogram of body weight serves to emphasize the point that physiologically optimal intake of a given food is not necessarily the greatest amount that can be handled by the alimentary tract. Still less do the results justify forcing high protein diets, as by addition of casein or lactalbumin, to the point of gastro-intestinal rebellion. The results obtained with children do not disprove for adults the usefulness of the rule of Peters and Bulger, whereby the protein fed is 75 Gm. plus the amount of protein lost in the urine; the amounts thus calculated are seldom above 1 to 1.5 Gm. per kilogram of body weight and may never exceed the usual assimilating optimum of adults. The author's data do not indicate that in the nephrotic syndrome the loss of protein in the urine is accompanied by compensatory increase in ability to assimilate food protein.

Cause of Death in Coronary Thrombosis.—To determine the incidence of pulmonary infarction as well as other causes of death, Eppinger and Kennedy review the records of 200 consecutive cases of coronary thrombosis proved by necropsy. The study shows that 32 per cent of the patients died suddenly; 53.5 per cent died of congestive heart failure and 14.5 per cent of other causes. Of the latter group, two died of mesenteric embolism and one of cerebral embolism. In addition to myocardial rupture, ventricular fibrillation and Stokes-Adams attacks, it was found that pulmonary embolism accounted for sudden death in 6.5 per cent of the cases. Among 107 patients dying of congestive heart failure, pulmonary embolism was the most important contributory cause of death in thirty-five (32.7 per cent). Embolism occurred in sixty-two cases (31 per cent), but in only forty-nine (24.5 per cent) did this complication affect the outcome of the disease.

American Journal of Tropical Medicine, Baltimore

17: 773-880 (Nov.) 1937

Proposed Revision of the Memorial Conference Classification of Leprosy. H. W. Wade, Culion, P. I.—p. 773.
Studies on Capacity of Various Brazilian Mosquitoes, Representing the Genera Psorophora, Aedes, Mansonia and Culex, to Transmit Yellow Fever. L. Whitman and P. C. A. Antunes, Bahia, Brazil.—p. 803.
Studies on Capacity of Mosquitoes of the Genus Hemagogus to Transmit Yellow Fever. P. C. A. Antunes and L. Whitman, Bahia, Brazil.—p. 825.
Recurring Clinical Activity in Infections with the McCoy Strain of Plasmodium Vivax. M. F. Boyd and S. F. Kitchen, Tallahassee, Fla.—p. 833.
Duration of Intrinsic Incubation Period in Falciparum Malaria in Relation to Certain Factors Affecting Parasites. M. F. Boyd and S. F. Kitchen, Tallahassee, Fla.—p. 845.
Employment of Multiply Infected Anopheles Quadrimaculatus to Effect Inoculation with Plasmodium Vivax and Plasmodium Falciparum. M. F. Boyd, S. F. Kitchen and W. H. Kupper, Tallahassee, Fla.—p. 849.
Simultaneous Inoculation with Plasmodium Vivax and Plasmodium Falciparum. M. F. Boyd and S. F. Kitchen, Tallahassee, Fla.—p. 855.
Study of Brucella Infection and Immunity in Humans. I. F. Huddleson, Myrtle Munger, East Lansing, Mich.; S. E. Gould and Doris Paulson, Eloise, Mich.—p. 863.

Archives of Pathology, Chicago

25: 1-148 (Jan.) 1938

Variations in Size, Weight and Histologic Structure of Thyroid Gland. L. E. Nolan, Minneapolis.—p. 1.
Chemical Reaction Between Oleic Acid and Aqueous Solutions of Magnesium: Its Pathologic Significance. P. J. Hartsuch, Chicago.—p. 17.
*Experimental Embolic Glomerulonephritis Produced with Human Fat, Fatty Acids and Calcium Soaps. C. S. Hagerty, University, Ala.—p. 24.
Experimental Tissue Lesions with Mixtures of Human Fat, Soaps and Cholesterol. E. F. Hirsch, Chicago.—p. 35.
Chemotropic Substance Derived from Normal Tissues. D. Silverman, Philadelphia.—p. 40.
*Cultural Studies on Relationship of Lymphocytes to Monocytes and Fibroblasts. J. W. Hall and J. Furth, New York.—p. 46.
Recent Contributions to Immunology of Helminthic Infections. J. T. Culbertson, New York.—p. 85.

Experimental Embolic Glomerulonephritis.—Hagerty produced lesions similar to those seen in diffuse glomerulonephritis in man in the kidneys of dogs and rabbits by injecting into the renal arteries emulsified oleic acid, liquid petrolatum and human fat, alone or containing calcium soaps. Two varieties of glomerular lesions were produced, dependent on the chemical composition of the fat. Mild fat irritants caused proliferation of endothelial cells and minimal growth of collagenous tissue. Strong irritants produced glomerular reactions in which there was swelling of endothelial cells and marked production of collagenous substance. Moderate irritants caused proliferation of endothelial cells and production of collagen. The various types of lesions in kidneys from patients with glomerulonephritis may represent alterations in response to irritants of different strengths. Fat may be an etiologic agent in the renal changes of Bright's disease.

Lymphocytes, Monocytes and Fibroblasts.—Hall and Furth investigated the conditions under which lymphocytes are thought to undergo transformation into monocytes and fibroblasts. The most significant of the experimental studies were made with the aid of tissue cultures, and in some of these material presumably containing lymphocytes alone, lymph of the thoracic duct, was used. The results of the experiments do not support the opinion of Bloom and other workers that lymphocytes of the thoracic duct are transformed in vitro into monocytes. Since monocytes were present in only small numbers in the cultures of the lymph of the thoracic duct, and fibroblasts were absent, it was desirable to determine whether the medium used was suitable for multiplication of monocytes and fibroblasts. From the fragments of the buffy coat of the blood, monocytes in great numbers migrated into the explant within twenty-four hours. In the splenic cultures, fibroblasts and histiocytes grew in large numbers. Monocytes appeared in the lymph cultures in variable numbers, depending on the number present before incubation. The great number of large lymphocytes in the lymph is noteworthy in this connection, for in fixed and stained preparations of tissue these cells can be distinguished from monocytes with difficulty. In the degenerating lymphocyte, the nucleus becomes homogeneous, the cytoplasm is more voluminous and the cell assumes an appearance similar to that of a blood monocyte. The percentage of monocytes in lymph varied from 0.14 to 0.6 (one tuberculous rabbit having 2.3 per cent).

Arkansas Medical Society Journal, Fort Smith

34: 157-182 (Jan.) 1938

*Anxiety States. T. A. Waters, New Orleans.—p. 157.
Sphenoid Sinusitis. R. Caldwell, Little Rock.—p. 163.
Prenatal Care. I. F. Jones, Fort Smith.—p. 167.

Anxiety States.—Waters states that in the anxiety state one sees a biologic reaction in which the whole personality reacts to some situation which threatens the patient's security and contentment. The symptoms are usually explained by the patient on the basis of "organic" disease, with serious import. This intensifies the symptoms and creates a vicious circle. In anxiety states one has to deal not only with the attacks but also with the part reaction, precipitating and predisposing causes and effects, which is the basis for the syndrome. After obtaining an account of the development of the present illness it is then necessary to gather more facts concerning the background out of which the present illness came into existence. When the patient's biography is completed, the physician is ready to give the patient an explanation and formulation of his condition. In a frank, matter of fact way he is told that his complaints have been given thorough consideration and that no "organic" condition can be held accountable for his symptoms; nevertheless they have a very definite cause, and he must therefore collaborate with the physician in order to work out his problems.

California and Western Medicine, San Francisco

48: 1-72 (Jan.) 1938

Microsurgery in Chronic Simple Glaucoma. O. Barkan, San Francisco.—p. 10.
Physical Phenomena Associated with Anxiety States: Hyperventilation Syndrome. W. J. Kerr, P. A. Gliebe and J. W. Dalton, San Francisco.—p. 12.
Diabetic Surgery: Ten Year Survey. I. Wills and P. A. Gray, Santa Barbara.—p. 16.
Medicine and National Policy. M. Fishbein, Chicago.—p. 21.
California Venereal Disease Control Program. M. H. Merrill, San Francisco.—p. 24.

Canadian Medical Association Journal, Montreal

38: 1-106 (Jan.) 1938

Salpingitis. B. Whitehouse, Birmingham, England.—p. 1.
Place of Radium in Treatment of Cancer. A. Lacassagne, Paris, France. —p. 9.
Pathologic and Immunologic Studies in Poliomyelitis. M. Brodie, Detroit. —p. 13.
Preeclampsia. W. P. Tew, London, Ont.—p. 20.
German Measles or Rubella. H. B. Cushing, Montreal.—p. 24.
Head Injuries. A. R. Elvidge, Montreal.—p. 26.
Surgical Treatment of Facial Injuries. F. Risdon, Toronto.—p. 33.
*Solution to Mystery of "Chronic Appendicitis." W. A. Bigelow, Brandon, Manit.—p. 36.
*Basal Pulmonary Lesions. H. R. Corbett, Kentville, N. S.—p. 38.
The Management of Esophageal Diverticula. W. O. Stevenson, Hamilton, Ont.—p. 42.
Diagnosis of Some Major Vascular Accidents. D. M. Baltzan, Saskatoon, Sask.—p. 45.
Some Complications Following Abdominal Operations. N. J. Maclean, Winnipeg, Manit.—p. 50.
Value of Mapharsen in Treatment of Congenital Syphilis. E. A. Morgan, Toronto.—p. 53.
Disturbances of Sebaceous Glands. W. R. Jaffrey, Hamilton, Ont.—p. 56.

Chronic Appendicitis.—Bigelow sent a questionnaire in January 1937 only to those 167 persons on whom appendectomy had been performed elsewhere, previous to operation at his clinic to cure a chronic pain in the right side of the abdomen and in whom the diagnosis had been made of "chronic appendicitis." None of the patients experienced any relief from the appendectomy performed. All cases in which acute appendicitis was diagnosed and operation performed were excluded. The patients were operated on by the author's usual method of complete removal of all so-called congenital bands and membranes from the cecum or ascending colon or hepatic flexure, or any combination of these present. Of the 147 patients who responded to this request, 136 reported complete relief from pain on the right side. This gives a result of 92 per cent cured by this operation.

Basal Pulmonary Lesions.—Corbett deals with the common diseases occurring in adults and stresses from a roentgenologic aspect the technic employed in bringing such cases to a diagnostic conclusion. Distortion and blurring from heart action and arterial pulsations are more prone to occur at the bases of the lungs. Fluoroscopically the lung tissues near the heart tend to follow the movements of the heart itself but lag behind the more rapid movements. The greatest lung movement is near the apex of the heart, and the excursion of the lung tissue at this point appears to be half that of the heart cycle (end of systole and beginning of diastole); the speed of the lung tissue is roughly one-eighth the maximal speed during the heart cycle. The intrascope or planigraph has the advantage of detecting and localizing pulmonary cavities. In the standard posteroanterior examination of the chest the cardiovascular shadow obscures the lung parenchyma occupying the inferior and medial margin of the left lung, including the retrocardiac area and the paravertebral quarter on both sides. The region can be demonstrated by films in the right and left oblique as well as the true lateral. Usually all cases are checked up fluoroscopically and if a lesion is suspected special films are taken.

Iowa State Medical Society Journal, Des Moines

28: 1-40 (Jan.) 1938

Hyperinsulinism and Hypoglycemia in Infants and Children. A. F. Hartmann, St. Louis.—p. 1.
Dangers in Use of Protamine Zinc Insulin. R. L. Jackson and J. D. Boyd, Iowa City.—p. 3.
Fulminating Meningococcic Septicemia with Bilateral Adrenal Hemorrhage. J. S. Weingart, Des Moines.—p. 5.
*Intrathoracic Goiter. K. L. Johnston, Oskaloosa.—p. 6.
Breast Tumors. G. Augustine, Council Bluffs.—p. 8.

Intrathoracic Goiter.—Johnston considers intrathoracic goiter as simply thyroid tissue within the superior mediastinal cavity, which is the space left in the thorax by the nonapproximation of the two pleurae and above the pericardial sac, behind the sternum and in front of the upper thoracic vertebrae. It is almost invariably adenomatous in nature. The effects are largely disturbances of pressure caused by a growing mass within a bony cage which cannot expand, and the proximity of this pressure to vital mediastinal structures. Toxic symptoms, the well known chronic thyrotoxicosis syndrome, may be present, but thoracic surgeons emphasize their secondary place in the picture and many authorities stress their rarity. This is essentially a disease beyond the fourth decade of life. The respiratory signs appear first and are constantly present. They begin as an effort dyspnea, which soon becomes a marked inspiratory stridor. A hacking cough and choking spells at night, which make suffocation seem imminent, appear. Hoarseness as a symptom has been variously interpreted. Circulatory signs are next in importance. They are primarily interference with the function of the blood vessel. Pressure on the thoracic vessels causes venous stasis of the thorax, leading to heart stasis, then cardiac dilatation, and myocardial degeneration. When the overburdened heart fails, auriculoventricular block or fibrillation occurs and death follows in typical congestive heart failure or by a sudden coronary accident. Tracheal deformity is manifest by curving or bowing from the normal midline position and by diminution in tracheal diameter in some axis, or in the change in the tracheal shape, and stereoscopy is often of great aid. Dysphagia is rare. Percussion of the upper anterior thorax may show dulness, but its absence is undependable. In the differential diagnosis of the condition aortic aneurysm, thymus tumor, Hodgkin's disease, intrathoracic dermoids, esophageal diverticulum, lung tumor, Pott's disease, mediastinitis and the asthmas must be considered. The treatment is surgical.

Kansas Medical Society Journal, Topeka

38: 501-540 (Dec.) 1937

Carcinoma of the Colon Complicated by Amebiasis. G. B. Kent, K. C. Sawyer and C. F. Kemper, Denver.—p. 501.
The Preservation of Bacteria Desiccated in a Vacuum at Room Temperature. N. P. Sherwood and L. L. Coriell, Lawrence.—p. 506.
The Management of Ureteral Calculi. V. L. Pauley, Wichita.—p. 509.
Diaphragmatic Hernia. M. Bernreiter, Kansas City.—p. 510.
Mental Symptoms in Brain Tumor: Review of Some of the Recent Literature. J. Pessin, Topeka.—p. 513.

Maine Medical Journal, Portland

29: 1-22 (Jan.) 1938

Graduate Medical Education in Maine. F. T. Hill, Waterville.—p. 1.
Case History. E. H. Drake and F. F. Ferguson, Portland.—p. 3.
Herpes Zoster Gangrenosus: Report of Case. I. F. Gregory, Bangor. —p. 7.

New England Journal of Medicine, Boston

218: 1-52 (Jan. 6) 1938

Hemolytic Streptococcus Infections, with Especial Reference to Prognosis and Treatment with Sulfanilamide. C. S. Keefer, Boston.—p. 1.
Encephalography in Diagnosis of Subdural Hematomas: Analysis of Thirty-Five Cases. T. J. C. von Storch and D. Munro, Boston.—p. 6.
Rectal Evipal Sodium as Basal Anesthetic in Urologic Surgery. J. H. Harrison and J. E. Dunphy, Boston.—p. 10.
What Massachusetts Does for Its Mental Defectives. N. A. Dayton, Boston.—p. 13.
Progress in Hematology in 1936. W. Dameshek, Boston.—p. 15.

West Virginia Medical Journal, Charleston

34: 1-48 (Jan.) 1938

Function of the Dentist in Prevention and Care of Intra-Oral Cancer. H. H. Ashbury, Elkins.—p. 1.
Magnetizable Intra-Ocular Foreign Bodies. I. D. Cole, Clarksburg.—p. 9.
Medical Aspects of Peptic Ulcer. A. S. Brady Jr., Charleston.—p. 13.
Peptic Ulcer. J. E. Cannaday, Charleston.—p. 15.
Apparent Synergism of Apomorphine and Morphine: Report of Case. G. R. Maxwell and G. A. Emerson, Morgantown.—p. 25.
*Dermatitis Eczematosa Due to Butesin Picrate. O. G. King, Bluefield. —p. 28.
Streptococcic Meningitis: Review of Case Treated Successfully with Sulfanilamide. T. G. Folsom, Huntington.—p. 33.

Dermatitis Eczematosa Due to Butesin Picrate.—Since minor household burns are frequent and sunburn has become a national prerequisite to good health, King reviews the reported cases of sensitivity to butesin picrate. He cites two cases and offers the theory that the lymphatics are probably concerned both before and after the drug or toxic agent reaches the blood stream. The patch test showed one of the patients to be sensitive to trinitrophenol and the other to butesin. The patient sensitive to trinitrophenol was hospitalized for two weeks and lost a total of fifty days from work, whereas the one sensitive to butesin spent four weeks in the hospital and was not able to work until after the sixth week. Treatment consisted of withdrawal of butesin picrate, rest in bed, symptomatic relief, wet dressings of 5 per cent tannic acid and boric acid ointment.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

Archives of Disease in Childhood, London

12: 339-406 (Dec.) 1937

Studies in Gastro-Enteritis. E. D. Cooper.—p. 339.
Studies in Anemia of Infancy and Childhood. L. G. Parsons, Evelyn M. Hickmans and Ethel Finch.—p. 369.
Continuous Intravenous Drip in Infants and Children. W. C. Black.—p. 381.

British Journal of Urology, London

9: 327-454 (Dec.) 1937

Three Unusual Primary Kidney Tumors. F. S. Patch.—p. 339.
Medical Treatment of Urinary Infections. D. M. Dunlop.—p. 359.
Carcinoma of Penis. G. S. Foulds and B. W. Stevens.—p. 368.

British Medical Journal, London

2: 1207-1260 (Dec. 18) 1937

Radiologic Aspects of Bone Tumors. R. E. Roberts.—p. 1207.
Progress of Diphtheria Prevention: Survey and Some Results. J. G. Forbes.—p. 1209.
Sex-Linked Microphthalmia Sometimes Associated with Mental Deficiency. J. A. F. Roberts.—p. 1213.
Modern Control of Scarlet Fever. W. R. F. Collis.—p. 1216.
*Vitamin E in Treatment of Habitual Abortion. D. Currie.—p. 1218.
*Pigeons as Possible Tetanus Carriers. A. W. Russell.—p. 1220.

Vitamin E in Treatment of Habitual Abortion.—Currie discusses the results in thirty-seven women who aborted more than once and whom henceforth he treated with wheat germ oil. Collectively these women had had 130 pregnancies and gave birth to only sixteen viable children. Under treatment there were thirty-seven living children. Two of them aborted, there were two sets of twins, and four children died in the hospital from prematurity. The appearance of albuminuria of pregnancy to a severe degree was a new problem that arose during treatment. Five patients showed gross signs of toxemia, in one it was necessary to induce labor by puncture of the membranes and in two cesarean section was carried out. In the majority of cases treatment was not instituted until after the twelfth week of pregnancy and yet the results show sufficient success for some credit to be ascribed to the use of the vitamin, even after complete placentation. Some observers consider that the vitamin is of value only in the early months. Naturally, some of these women might have gone to term unaided, as did two who failed to return until they were in labor. Wheat germ oil has also been given with success in cases of threatened abortion. Fifteen of these have been so treated and fourteen taken successfully to term. Along with the administration of the vitamin the other recognized methods of treatment were used.

Pigeons as Possible Tetanus Carriers.—Russell cites a fatal case of tetanus in a child of 18 months. The incubation period was twenty-four hours at the most and death ensued in about forty-four hours from the onset of the illness. The typical clinical signs were exhibited and large doses of antitetanus serum intramuscularly and intrathecally were given at the earliest opportunity. The subsequent investigation seems to implicate a pigeon (or pigeons) as a "carrier" of tetanus. No animals were available for inoculation tests with the tetanus bacilli obtained on culture from the pigeon's droppings, but the evidence otherwise would suggest the following chain of events: 1. The pigeon became infested with tetanus bacilli, probably by pecking horse manure, and became a "carrier," passing the bacilli or spores in its droppings, although showing no sign of illness itself. 2. The droppings infected the ground below the pigeon loft. 3. The child playing on the ground became infected through the skin, which was broken and scratched, as the result of active scabies. 4. The child developed clinical tetanus and died after a brief illness.

East African Medical Journal, Nairobi

14: 281-310 (Dec.) 1937

Traumatic Rupture of Gallbladder: Report of Case. M. A. W. Roberts.—p. 283.
Esophageal Hiatus Hernia: Case. J. F. Q. Conolly and W. G. S. Hopkirk.—p. 287.
Achondroplasia in Kenya Native. F. J. Wright.—p. 289.
Birth per Rectum: Case. P. G. Preston.—p. 290.

Indian Medical Gazette, Calcutta

72: 713-776 (Dec.) 1937

Gnathostomiasis in Human Beings. P. A. Maplestone and N. V. Bhaduri.—p. 713.
Organization of Blood Transfusion Service in District Hospital. P. C. Dutta.—p. 715.
Electrocardiographic Changes in Beriberi. T. K. Raman.—p. 717.
*Use of Tea in Treatment of Burns. M. V. P. Peiris.—p. 718.
Use of Cod Liver Oil in Infected Wounds. B. Chatterjee.—p. 721.
Interatrial Septal Defect with Mitral Insufficiency of Congenital Origin. P. Kutumbiah and P. Ramachandra Rao.—p. 722.
Color Chart for Determination of Hydrogen Ion Concentration. C. L. Pasricha and S. Ghosh.—p. 725.
Experimental Investigation into Duration of Tolerance to Reinfection in Monkey Malaria. B. M. Das Gupta.—p. 726.
Renal Efficiency in Glaucomatous Patients. J. N. Jaswal.—p. 728.
Clearance of Pistia Stratiotes as Control Measure for Filaria Malayi Infection. W. C. Sweet and V. Madhavan Pillai.—p. 730.
Effect of Reduced Pressure Combined with Increased Temperature on Viability of Bedbugs and of Their Eggs. E. Somasekhar.—p. 734.
Sanitary Improvements Through Village Health Leagues. K. Prasada.—p. 737.

Use of Tea in Treatment of Burns.—Peiris advises the use of tea in the treatment of burns. A pot of tea is prepared by infusing six teaspoonfuls of black tea in six cupfuls of boiling water for ten minutes. Four layers of clean handkerchiefs or sheeting are soaked in the hot tea and the warm compresses are applied directly to the burned area. A light bandage is applied over it. The bandage is soaked with tea when it gets dry during the first twenty-four hours. The dressing is left on for from twelve to fourteen days. The constitutional treatment is carried out in the usual way. Antitetanic serum is given on the first day. If at any time there is sepsis as evidenced by a rising temperature, rapid pulse, coated tongue and anorexia, the dressings are reapplied after the wound has been cleansed thoroughly under an anesthetic. In the place of compresses, spraying with tea may be carried out every hour for from twelve to twenty-four hours as in the case of tannic acid. An electric cradle will help the applications to dry. Cutaneous grafting is necessary for the large ulcers of deep burns. During the last six months the author has treated twelve cases of burns. Six were extensive third degree burns. The early cases were treated with compresses of moist tea leaves remaining in the ward teapot. The burnt areas healed as rapidly with tea compresses as with tannic acid compresses. There were no deaths.

Lancet, London

2: 1469-1522 (Dec. 25) 1937

Some Principles of Child Discipline. R. Miller.—p. 1469.
Blood Chemistry in Intestinal Obstruction: Changes in Response to Treatment. M. A. Falconer and A. Lyall.—p. 1472.
*Observations on Complement Fixation Test in Psittacosis. S. P. Bedson.—p. 1477.
Acute Silicosis in Lead Miners. R. W. Thomas, with note on histology by S. L. Cummins.—p. 1481.
Standardization of Extracts of Suprarenal Cortex. G. Török and L. Neufeld.—p. 1485.

Complement Fixation Test in Psittacosis.—Bedson has prepared a psittacosis antigen from a crude virulent mouse-spleen suspension by centrifugating out the virus, resuspending it in phosphate buffer and heating the suspension for thirty minutes at 212 F. This heated antigen has been found superior to the crude virus suspension for carrying out complement fixation tests with the serums from patients with human psittacosis. The advantages of the heated antigen are that it makes the test more delicate, that it is not dangerous to handle and that it is stable.

Bull. of Health Org., League of Nations, Geneva

6: 299-504 (June) 1937

Report on Popular Nutrition in Chile. C. Dragoni and E. Burnet.—p. 299.
The Milk Problem: Critical Study of Its Nutritional, Hygienic, Economic and Social Aspects. H. C. Bendixen, G. J. Blink, J. C. Drummond, A. M. Leroy and G. S. Wilson.—p. 371.

Chinese Medical Journal, Peiping

52: 623-790 (Nov.) 1937

Traumatic Stricture of the Male Urethra. K. H. Wang and G. Y. Char.—p. 623.
Obstetric Criteria in North China: I. Analysis of Antenatal Findings. G. King and C. M. Yueh.—p. 639.
Schistosomiasis Japonica in Nanking. C. F. Chu.—p. 651.

Presse Médicale, Paris

46: 73-96 (Jan. 15) 1938

Ocular Pain and Photophobia. A. Magitot.—p. 73.
*Remarks on Gangrenes of Exanthematous Typhus. M. Costantini, Liaras and Bourgeon.—p. 75.
Tuberculosis Localized in Rhinopharynx and Compressing Soft Palate. Z. Cheridjian and T. Scicolounoff.—p. 76.

Gangrene in Exanthematous Typhus.—Of the surgical complications of exanthematous typhus, Costantini and his associates wish to discuss only gangrene, especially the gangrene of the skin and of the extremities. The moist type is progressive and it is difficult to decide to what extent amputation is necessary. Dry gangrene is characterized by a rapid arrest of the process of extension. This arrest is characterized by a furrow, which separates the dead from the living tissue. The natural process traces with precision the way which should be followed by the bistoury and the saw. This makes possible economical interventions in contradistinction to the great sacrifices that become necessary in the hasty interventions required in moist gangrene. Posttyphic gangrene is of the dry type, involving either an extensive portion of the skin or a portion of the extremities. Generally the gangrene involves a lower limb, but an illustration is shown in which the posttyphic gangrene involves an arm. When the skin alone is involved, transformations occur which result in a black dried plaque with clear-cut borders. This plaque is cast off and the resulting wound is rapidly covered with epidermis. The scar is soft and the surrounding skin appears well perfused. It may happen that the gangrenous cutaneous zones do not involve the fat of the skin. Then the blackish patch can be detached without much effort or becomes detached spontaneously and the tissues underneath already show considerable epidermization. The authors further discuss posttyphic gangrene of the toes, of which two illustrations are shown. Discussing the pathogenesis of the gangrene in exanthematous typhus, they direct attention to the nodules of Franckel, which are specific for typhus. These nodules are found in the central nervous system, in the myocardium and under the epicardium, but their site of predilection is around the vessels. If they cause obliteration of the vessels, gangrene will result. The authors discuss the surgical treatment of the gangrene of exanthematous typhus. They stress two points: 1. There should be no haste; it is advisable to wait the time that is necessary for the development of the spontaneous separation between the living and dead tissues. 2. The knife or the saw should follow the furrow of demarcation.

Schweizerische medizinische Wochenschrift, Basel

68: 37-56 (Jan. 8) 1938

Progress in Insulin Therapy. H. C. Hagedorn.—p. 37.
*Question of Primary Tuberculosis of Tonsils. E. Schlittler.—p. 42.
Physiologic Observations in Treatment of Paralysis of Recurrent Nerve. K. Kistler.—p. 44.
Influence of Radium and of Radon on Normal Cell and Cancer Cell. T. Gordonoff and F. Ludwig.—p. 45.
Breast Feeding in Switzerland. Imboden-Kaiser.—p. 47.

"Primary" Tuberculosis of Tonsils.—Schlittler says that four years ago he reported about ninety-eight cases of tuberculous lymphomas of the neck in which tonsillectomy was done. Microscopic examination of the tonsils revealed a tonsillar tuberculosis in forty-eight cases. He assumed that the process in the tonsils was a primary infection with subsequent secondary infection of the adjoining lymph nodes, for the following reasons: (1) the fact that the majority of the patients (63 per cent) were less than 12 years old, (2) the fact that in 73 per cent of the cases only one tonsil was involved, (3) the localization of the lymphomas, (4) the behavior of the lymphomas after tonsillectomy (disappearance in 70 per cent of the cases) and (5) the fact that the absence of clinical signs of a pulmonary tuberculosis seemed to contraindicate a sputogenic tuberculosis, while a hematogenic secondary tuberculosis seemed to be contraindicated by the absence of other forms of tuberculosis. During the last four years the author observed forty-one additional cases of chronic or subacute lymphadenitis of the neck in which tonsillectomy was done. The examination of the tonsils in this series revealed tuberculosis in all cases. The author says that observations on this second series of tonsils have modified his opinion about the pathogenesis of tonsillar tuberculosis. As regards the age factor, this second series differed from the first in that the size of the age groups of patients above and below 12 years was exactly the opposite. Moreover, the unilateral involvement of the tonsils was not as frequent as had been the case in the first series, and thus it seems no longer justified to assume that a hematogenic infection is less probable than a primary infection of the tonsils. On the basis of these and other considerations, the author suggests that perhaps the greatest majority of the eighty-nine cases of histologically demonstrated tonsillar tuberculoses were not primary tuberculous processes but new infections or secondary infections of hematogenic origin. However, he thinks that further investigations will be necessary to determine the exact percental incidence of definitely primary, postprimary (new infection) or secondary hematogenic forms of tonsillar tuberculosis.

Folia Medica, Naples

23: 1151-1206 (Nov. 15) 1937

*Action of Extracts of Spleen on Hematopoietic Organs and Endocrine Glands. R. del Zoppo.—p. 1153.
Volume of Liver During Experimental Necrosis of Right or Left Ventricle. A. Rubino.—p. 1166.
Postantiserum Local Tetanus and Tetanus Prevention. M. Mauro.—p. 1178.

Action of Extract of Spleen on Hematopoietic Organs.—Del Zoppo made histologic studies on the hematopoietic organs and endocrine glands of young normal rabbits of both sexes which had had a hypodermic injection of 8 or 12 Gm. of splenic extract for each kilogram of body weight. The extract induced slight hyperplasia of the thyroids and of the anterior lobe of the hypophysis, moderate hyperplasia of the bone marrow with predominant proliferation of granulocytes, intense hyperplasia of the lymph nodes and of the lymphatic tissue, especially of the spleen, and degeneration of the parenchyma of the liver and of the pancreas and of the acinous tissues of the pancreas. The kidneys, adrenals and genital glands were not modified. The author's results are in conflict with those reported by Torrioli and Pusic as to the inhibiting or stimulating action of extracts on the bone marrow. Probably the conflicting results show that the effect of the extract depends on the dose and route of administration. Small doses administered hypodermically, such as were used by the author, stimulate moderately the bone marrow and intensely the lymphatic structures. Large doses of the splenic extract, administered intravenously (Torrioli and Pusic), cause hyperplasia of the reticulo-endothelium and secondary aplasia of the bone marrow. The extract has also a toxic effect on the pancreas and the liver.

Prensa Médica Argentina, Buenos Aires

25: 1-56 (Jan. 5) 1938. Partial Index

Value of Contrasting Methods in Roentgenography of Joints. R. A. Marotta and F. M. Bustos.—p. 1.
Chemotherapy in Tuberculosis in Children. A. A. Raimondi and A. Sangiovanni.—p. 7.
*Congenital Valvular Obstruction of Posterior Urethra in Infant: Case. D. Brachetto-Brian, E. C. Brewer and Sara de Lazaga.—p. 12.
Multiple Subcutaneous Nodules in Cancer of the Lung. E. S. Mazzei, J. M. Remolar and R. Latienda.—p. 37.
Roentgenology of Perinephritis. N. B. Turco.—p. 43.
Osteosynthesis: Use of Small Nails. E. Finochietto.—p. 46.

Obstruction of Posterior Urethra.—Brachetto-Brian and his collaborators report a case of general dilatation of the urinary tract from congenital valvular obstruction in an infant, aged 5½ months. The mother had pulmonary tuberculosis but the son was soon taken away from her. The tuberculin reaction and the roentgen examination of the lung gave negative results for tuberculosis. He showed progressive nutritional disturbances, great distention of the abdomen without gastro-intestinal symptoms and painful, difficult micturition. Later on anemia, vomiting, diarrhea, nervousness and terminal bronchopneumonia developed. At necropsy a membranous valve was found at the posterior urethra, which caused permanent retention of urine with consequent dilatation of the urinary tract. The bladder had no neck. The prognosis depends on early treatment. The most frequent early symptoms are infection and latent uremia. Roentgen examination shows the fundus of the bladder in the form of a funnel. Nutritional disorders of unknown etiology, pain and distention of the abdomen and painful micturition with a small stream in children are suggestive of valvular obstruc-

tion of the neck of the bladder. Removal of the valves results in restoration of normal micturition. Satisfactory results are reported in the literature from the use of the "cautery punch" in the treatment of the condition in young children.

Deutsches Archiv für klinische Medizin, Berlin

181: 229-348 (Dec. 11) 1937. Partial Index

*Investigations on Development of Extrasystoles by Interference of Two Rhythms. P. Eckey.—p. 229.
Clinical Observations on Several Abnormal Postinfectious Vascular Reactions and Their Relations to Allergy. H. Weselmann.—p. 257.
*Studies on Basal Metabolism During Artificial Fever. E. Schäfer-Fingerle.—p. 268.
Studies to Clarify Sudden Death During Swimming Contest. E. J. Klaus.—p. 275.
Clinical Syndrome: Narcolepsy with Obesity and Polyglobulism in Its Relation to Cushing's Disease. Annie Spitz.—p. 286.
Observations on Secretion of Fasting Stomach During and After Treatment with Jejunal Catheter. F. Maret.—p. 305.
"Premature Lymphocytic Phase of Cure" in Diphtheria and Scarlet Fever Following Specific Serotherapy. H. A. Heinsen and H. Biedenkopf.—p. 318.

Extrasystoles Produced by Interference of Two Rhythms.—Eckey says that the opinion that extrasystoles are the manifestation of an impairment of the cardiac muscle failed to correspond to the clinical aspects in many cases. For this reason other possibilities were considered, and there are two theories which have especial importance for the development of extrasystoles. The first one is the circle theory of de Boer, according to which the extrasystole is causally connected with the preceding normal beat. The second theory is that of Kaufmann and Rothberger, who regard extrasystole as an interference manifestation of two rhythms. Eckey points out that by comparing the various theories and by considering that one theory may explain one characteristic of an extrasystole and another theory another, it must be concluded that extrasystoles are not a uniform disorder. It is still doubtful whether the existing theories will explain all cases of extrasystole. He reports three cases which throw light on the interference theory. He demonstrated that the extrasystoles, which apparently were scattered at random into the electrocardiographic curves, were the result of the interference of a special ventricular stimulation center with the sinus rhythm. It could be demonstrated that an increase in the tonus of the vagus has an inhibiting effect on the ventricular center, whereas a decrease in this tonus has a stimulating effect. This possibility had formerly been denied. The author demonstrated also the incorrectness of the opinion that the cessation of the extrasystole is a result of changed interference conditions following alteration of the sinus frequency by work or the stimulation of the vagus. He could prove that work as well as pharmacologic stimulation of the vagus, by inhibiting the special stimulation center, leads to a reduction in or to the complete disappearance of the extrasystole.

Basal Metabolism During Artificial Fever.—Schäfer-Fingerle says that investigations on the metabolic processes during fever have demonstrated that the increase in temperature is nearly always accompanied by a more or less pronounced increase in oxidation. However, observations during recent years have shown that infections may produce the same metabolic disturbances independent of the development of fever. This fact had long been known about afebrile tuberculosis, but the same phenomenon can be observed in some disorders caused by colds, in sepsis lenta and so on. Moreover, in malaria therapy it was observed that an increase in oxidation is already noticeable before the fever has developed. In connection with the therapeutic use of fever the question arises whether the therapeutic action is exerted by the fever as such or by the increase in the metabolic processes connected with it. In order to throw light on this problem, the author decided to study the metabolic and fever reactions produced by the various substances that are used in the production of therapeutic fever, such as bacterial proteins of apathogenic bacteria and autovaccine. He found that, following the administration of these substances, an increase in oxidation takes place independently of the fever reaction. In cases in which it was possible to produce an increase in the metabolism independently of the fever reaction, the general effect was the same as after a temperature reaction. To be sure, in the course of repeated injections it is no longer possible to separate the increase in the metabolic rate from the fever reaction, and it is consequently difficult to decide whether the therapeutic action is entirely determined by the increase in metabolism.

Bibliotek for Læger, Copenhagen

129: 401-433 (Dec.) 1937

*Endemic Infection with Paratyphoid B Bacillus Fermenting Dextrotartaric Acid at Hospital for Insane. K. Bojlén, C. Clemmesen and Margrete Lomholt.—p. 401.

Infection with Paratyphoid B Bacillus Fermenting Dextrotartaric Acid.—The picture in the pronounced cases in this endemic at St. Hans Hospital from November 1934 to May 1937, described by Bojlén and his associates, was that of an acute gastro-enteritis, but the cases were mild. There was acute gastro-enteritis in twenty-eight cases, afebrile diarrhea in thirty-six and "silent" infection in seventy-three. In four cases the fetal outcome is attributed to the infection and in five the infection is regarded as a possible contributing cause of death. In feces tests made extensively at the hospital for many years in cases of intestinal disorders the dextrotartaric acid-positive paratyphoid B bacillus was never before isolated. In the thirteen scattered cases of infection with the bacillus in question discussed by Martin Kristensen in the *Bibliotek for læger,* November 1937, page 390, four sharply defined types of the bacillus were found. In the hospital endemic the bacilli were all of one of these types. In the authors' opinion the endemic was most likely introduced by a chronic bacillus carrier, a convalescent carrier or a patient with acute infection and continued by new acute cases, convalescent carriers, patients with "silent" infection and chronic bacillus carriers, spreading in spite of precautionary measures which had been effective in the fight against "institutional diarrhea." The bacteria appeared to be of low virulence which could, however, under certain conditions change character. The cases are tabulated in detail.

Hospitalstidende, Copenhagen

80: 1245-1280 (Nov. 30) 1937

Reactivity of Thrombocyte System. S. Heinild.—p. 1245.
*Polycythemia Vera: Hypothesis Concerning Its Gastrogenic Pathogenesis Together with Case in Which Treatment Consisted of Gastric Lavage and Diet. E. Mogensen.—p. 1271.

Polycythemia Vera.—Mogensen says that, while the concept of polycythemia vera as a "plus variant of the gastric function as against the minus variant pernicious anemia" may not seem to be strongly founded, the promising results reported after treatment with gastric lavage and diet or with diet alone call for further attempts with such treatment. In his patient, with a red cell count of 10,000,000, daily treatment for five months with gastric lavage and diet according to Morris was without effect. Later treatment for four weeks with a diet low in animal protein according to Herzog was also ineffective. He interprets the negative results in this case as an indication that the disorder termed polycythemia vera may include different pathogenic identities.

80: 1281-1320 (Dec. 7) 1937

*Investigation on Liver Function in Certain Skin Diseases with Remarks on Etiology and Treatment. V. Genner and T. K. With.—p. 1281.

Liver Function in Skin Diseases.—Genner and With applied Bauer's galactose test, Roma's lipase test, determination of the icterus index (Meulengracht) and series determination of the urobilinogen (Ehrlich) and bile acids (Hay) in the urine of 365 patients, of whom 104 had lupus vulgaris, seventy-four psoriasis, 102 eczema, fifty-nine pruritus and prurigo and twenty-six prurigo Besnier. They assert that their results do not support the assumption of an endogenic disturbance in metabolism as the cause or the result of these skin diseases. Numerous factors indicate that prurigo as well as eczema depends chiefly on the effect of external noxae in connection with individual peculiarities of the skin which make it especially susceptible. The basis for the frequent more or less rigorous diet therapy in these cutaneous disorders is therefore considered too meager to justify its imposition.